

**THE PHYSIOLOGICAL EFFECTS OF BLOOD FLOW RESTRICTED MUSCLE  
STIMULATION**

**A Thesis**

**Submitted to the Graduate Faculty  
in Partial Fulfillment of the Requirements  
for the Degree of Master of Science  
Human Biology**

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## ABSTRACT

Emerging evidence suggests that low load exercise stimuli can lead to significant muscular adaptations when blood flow to a muscle is restricted or occluded. Electrical muscle stimulation has been used for years in the rehabilitative settings, but muscular hypertrophic or oxidative adaptation resulting from electrical stimulation is typically of limited magnitude, likely owing to the discomfort caused by the high intensity stimulus necessary to cause greater adaptation. Combining low intensity transcutaneous electrical muscle stimulation (TEMS) with blood flow restriction (BFR) has yet to be examined, and offers the potential to stimulate substantial muscular adaptation without undue discomfort. We examined the effects of combining BFR with a low intensity TEMS on the upper and lower body musculature. Twenty recreationally active subjects ( $24 \pm 6$  yr,  $174 \pm 10$  cm,  $70 \pm 17$  kg) were recruited and had every limb randomly allocated to one of four possible training groups: 1) BFR -4mins inflated, 4 mins deflated at 220mmHg alone, 2) TEMS alone- at a maximally tolerable intensity, 3) BFR+TEMS (COMB), or 4) control (CON). Each arm and leg was “trained” in its respective intervention group four times weekly for six weeks. To test muscular adaptation, muscle size and strength were measured at baseline and following 6 weeks of stimuli. Mean differences in size (g) and strength (kg), between week 0 and week 6, were calculated for each intervention group. **ARM:** After 6 weeks of training, the COMB group changed by  $45 \pm 201$  g and  $3.2 \pm 3.6$  kg, whereas the BFR group changed by  $21 \pm 103$  g and  $2.6 \pm 3.9$  kg. The TEMS group changed by  $-37 \pm 121$  g and  $0.7 \pm 3.0$  kg; while the CON group changed by  $4 \pm 78$  g and  $0.6 \pm 2.9$  kg. There was no significant difference between groups for maximal strength ( $p=0.2$ ) or size ( $p=0.4$ ). **LEG:** Leg strength changed by  $32 \pm 19$  kg in the COMB group and was significantly different than the  $3 \pm 11$  kg change in the CON group ( $p=0.03$ ). The TEMS and BFR group changed by  $16 \pm 28$  kg and  $18 \pm 17$  kg, respectively. There were no other significant differences between groups. Leg size changed by  $95 \pm 238$  g in the COMB group; whereas size changed by  $79 \pm 439$  g and  $26 \pm 387$  g in the TEMS and BFR groups, respectively. The CON group changed by  $-83 \pm 279$  g. There were no significant differences between groups for leg size. The results suggest no effect of the intervention, however, despite a relative lack of overall statistical significance, owing to large individual variability in response, there is an indication of a possible effect. The absence of significance in most comparisons is likely explicable by the high inter-individual variability and differential adaptive responses.

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## **LIST OF ABBREVIATIONS USED**

ACSM: American College of Sports Medicine

BFR: Blood Flow Restriction

COMB: The intervention group that combined blood flow restriction and transcutaneous electrical muscle stimulation.

CON: Control group

CSA: Cross Sectional Area

DEXA: Dual Energy X-ray Absorptiometry

LMSD: Lower Leg Strength Device

RM: Repetition Maximum

TEMS: Transcutaneous Electrical Muscle Stimulation

# CHAPTER 1: INTRODUCTION

## 1.1 Significance

It is well documented that in order to maintain muscle health, relatively high intensity exercise must be undertaken. The American College of Sports Medicine (ACSM)<sup>1</sup> recommends an exercise intensity of at least 70% One Repetition Maximum (1RM) to stimulate gains in muscular strength and hypertrophy, as it is understood that anything below this intensity rarely produces muscle growth or strength. This is because during resistance exercise, motor units are recruited according to the size principle<sup>2</sup>. Motor units and individual muscle fibers are recruited such that smaller motor units associated with type I fibers (also known as “slow twitch oxidative fibers”) are activated initially at low intensities, and larger motor units with type II (“fast twitch”) muscle fibers are recruited at higher exercise intensities with an increasing level of contractile force. In order to increase muscle mass and strength, it is important to activate type II muscle fibers during training, since these fibers have been shown to be more responsive to hypertrophy than type I fibers<sup>3</sup> and are generally larger. This is the reason for the suggestion of only moderate-high intensity resistance exercise being capable of inducing gains in muscle strength and size.

The gains in strength with high intensity resistance training are, undoubtedly, due to a combination of neurological and morphological factors. The increases in muscular strength during the **initial periods (0-3weeks)** of resistance training are not associated with changes in cross sectional area of the muscle; rather, they are due to changes in neural adaptations<sup>4</sup>. Motor units are generally recruited asynchronously, that is they are

not called on at the same time, but as they are needed to produce more force. They are controlled by multiple different neurons that can either transmit excitatory or inhibitory impulses, and whether the muscle contracts or not depends on the summation of many impulses received by a given motor unit at a given time. The motor unit is activated and contracts only when the excitatory impulses exceed the inhibitory impulses, and the threshold is met<sup>2</sup>. Strength gains occur when there are changes in connections between motor neurons. This allows for a more synchronous activation of the motor unit, facilitating contraction and resulting in an increased ability for the muscle to generate force<sup>2</sup>. **Longer-term (>3weeks)** changes in strength are more likely attributable to an increase in the size of the muscle fibers<sup>4</sup>.

This longer term increase in the size of muscle is referred to as hypertrophy. The increase in muscle size or “pump” one feels following a single bout of exercise is referred to as transient hypertrophy, and is attributable to fluid accumulation, or edema, in the intracellular and interstitial spaces of the muscle<sup>2</sup>. In contrast, chronic hypertrophy refers to the increase in muscle size associated with long-term resistance training. This reflects actual structural changes in the muscle that can result from an increase in the size of existing individual muscle fibers. It is hypothesized that there are three primary mechanisms for muscular hypertrophy: 1) mechanical loading, 2) muscle damage, and 3) exercise-induced metabolic stress, also known as the metabo-reflex<sup>5</sup>. Mechanical induced tension produced by force generation and stretch is considered essential to muscle growth. It is thought that tension disturbs the integrity of the muscle resulting in molecular and cellular responses in myofibrils and satellite cells<sup>6</sup>. Resistance training

can also result in localized damage to muscle tissue, which under certain conditions can produce hypertrophic responses. The response to myotrauma is very similar to an inflammatory response. Once damage is perceived, macrophages and lymphocytes migrate to the site and cause an inflammatory cascade. This results in the release of various growth factors and the proliferation and differentiation of satellite cells<sup>7</sup> . Numerous studies support an anabolic role of exercise-induced metabolic stress<sup>8</sup> and some investigators have speculated that metabolic stress may be of more importance than force development in eliciting hypertrophic responses<sup>9</sup> . Metabolic stress is established as a result of exercise relying on anaerobic metabolism for ATP production, which causes a build-up of metabolites such as lactate, hydrogen ions, inorganic phosphate, creatine, and others<sup>10</sup> . The metabolic stress-induced mechanisms thought to facilitate hypertrophy include hormonal shifts, cell swelling, free radicals, and increased muscle fiber recruitment and growth-related transcription factors<sup>11</sup> .

The maintenance and promotion of skeletal muscle mass and strength is essential for maintaining one's quality of life. Not only is skeletal muscle crucial for functional movement, but skeletal muscle also plays a vital role in maintaining normal glucose homeostasis and regulating whole-body glucose metabolism<sup>12</sup> , lipid oxidation<sup>13</sup> , and is one of the greatest modifiable contributors to the resting metabolic rate<sup>14</sup> . The maintenance of skeletal muscle becomes increasingly important with aging, as low levels of muscle mass are strongly correlated with a loss of functional independence, mobility and an increased risk of disability and functional impairment<sup>15</sup> . The high-intensity exercise required to induce muscle adaptation may not be practical for elderly people.

Other groups of people who may be unable to withstand the high stresses of heavy training include those recovering from injury or those with chronic health conditions. Therefore, it is very intriguing that emerging evidence suggests that low load exercise stimuli (i.e. <25% maximal capacity) can lead to significant muscular adaptations, when blood flow to a muscle is restricted or occluded<sup>16</sup>. To date, research has primarily focused on exercise using light weights<sup>4</sup> or aerobic-type exercise such as treadmill walking<sup>17</sup>. These findings are very encouraging as they suggest that persons for whom traditional high load training may be too difficult could adopt a lighter load for training, in combination with blood flow restriction (BFR), to stimulate increases in muscle size and strength effects. This training load would be much more suitable for the aforementioned persons.

Performing exercise while occluding muscle blood flow is a patented training method called blood flow restriction training or “Kaatsu Training” (literally “added pressure” in Japanese) developed by Dr. Yoshiaki Sato<sup>18</sup>. This technique is based on the compression of vasculature proximal to the exercising muscle by some sort of external compression device (i.e. a blood pressure cuff or a tourniquet). This reduced blood flow is thought to promote blood pooling in the capillaries within the local limb musculature, and induce an ischemic environment that enhances the metaboreflex in exercising muscle and thus the training adaptation, leading to increase muscle mass and strength<sup>18</sup>.

Despite many groups of people potentially benefitting from the muscular adaptations elicited by low-intensity exercise combined with blood flow occlusion, there are many

other groups of people who would be too weak or immobilized to undergo exercise even at low intensity. In the past, a technique called transcutaneous electrical stimulation (TEMS; electrical currents applied through the skin to evoke muscle contractions) has been used to prevent muscle atrophy during prolonged periods of immobilization, as TEMS has the potential to promote synthesis of muscle protein. Despite the potential of TEMS as a strength-training tool for the healthy, habilitative and rehabilitative, there is a general lack of agreement among the scientific community about its efficacy<sup>29</sup>. One of the main limitations of TEMS for stimulating large alterations in strength and hypertrophy is the excessive discomfort caused by the muscle contraction inducing electrical stimulus<sup>19</sup>. This is reinforced when considering the ability to tolerate high current intensities (and therefore to generate a stronger contraction) seems to be correlated with the effectiveness of TEMS<sup>20</sup>. Therefore, muscular adaptation as a result of electrical stimulation is limited owing to the discomfort caused by the high intensity stimulus necessary to cause greater adaptation.

The discomfort caused by the high-intensity electrical stimulus could conceivably be overcome by combining a relatively low-intensity electrical stimulus with an augmented training environment created through the use of blood flow occlusion. Just as blood flow occlusion allows for a lower intensity exercise to produce substantial muscular adaptations, blood flow occlusion could possibly also allow for a lower intensity electrical stimulus to produce substantial muscular adaptations, thereby decreasing the impeding discomfort. The combined (perhaps synergistic) effect of these two stimuli has yet to be examined.

## **1.2 Objective**

Therefore, the aim of this study was to examine the effects of combining blood flow restriction with a low intensity electrical stimulus on specific musculature of the upper body and lower body

## **1.3 Hypothesis**

A combination of BFR and TEMS will lead to greater muscular adaptations than either TEMS or BFR alone. BFR alone will lead to greater muscular adaptations than TEMS alone.

## **CHAPTER 2: LITERATURE REVIEW**

### **2.1 Blood Flow Restriction (BFR)**

The evidence for occluding blood flow while exercising has yet to be systematically reviewed and analyzed using meta-analytic techniques. Therefore, as a portion of my graduate work I have performed a systematic review of the literature to quantify the effectiveness of blood flow restricted exercise on muscle strength and hypertrophy. The full systematic review, “*The efficacy of blood flow restricted exercise for stimulating adaption in strength and hypertrophy: a systematic review and meta-analysis*,” has been submitted for publication, and can be found in Appendix D.

### **2.2 Safety of Blood Flow Restriction (BFR)**

After numerous studies have demonstrated the efficacy of blood flow restricted training, the literature now has shifted more toward the overall safety issues of this training.

Leonneke et al. (2011)<sup>58</sup> have provided an updated review on several measures of safety with respect to BFR. The following is a summary of this review.

BFR introduces obvious potential safety concerns with post-exercise blood flow, as blood flow dynamics are manipulated with BFR training. Studies investigating blood flow post-exercise is sparse but in summation, the peripheral blood flow response to BFR training appears to respond in a similar fashion to regular exercise.

Coagulation activity does not appear to increase following low-intensity blood flow restriction training, but in contrast fibrinolytic potential appears to be enhanced with blood flow restriction exercise, as it is with traditional resistance exercise. In addition, oxidative stress has not been shown to increase in response to BFR training; however the



research on this topic is sparse. Finally, BFR does not seem to have a chronic negative effect on nerve conduction velocity in healthy human subjects. The review concludes with a statement on how the current research on blood flow restriction exercise, when used in a controlled environment and experienced personnel provides a safe training alternative.

### **2.3 Transcutaneous Electrical Muscle Stimulation (TEMS)**

Transcutaneous electrical stimulation (TEMS) is a technique that consists of superficially generating action potentials to induce muscle contractions with a stimulation device connected to the surface of the skin with electrodes<sup>21</sup>. TEMS creates muscle fiber contractions by creating a current between two surface electrodes, from anode to cathode<sup>22</sup>. In recent years, much attention has been paid to TEMS due to its application potential as an assessment tool for neuromuscular function of muscles<sup>23</sup>, but more importantly it can act as a strength training tool for the healthy<sup>24</sup> and the individuals undergoing rehabilitation<sup>25</sup>. However, there is a general lack of agreement among the scientific community about its effectiveness, so any use of TEMS is met with a high degree of caution.

TEMS has the potential to preserve muscle-protein synthesis and prevent muscle atrophy during prolonged periods of immobilization<sup>26</sup>. However, the effectiveness of this rehabilitation procedure or strength training procedure remains to be clearly proven. Muffiuletti et al. 2013<sup>29</sup>, performed a formal systematic review of the literature to determine the rehabilitative effect of TEMS on skeletal muscle strength and mass in critically ill patients, in comparison with standard care. Ultimately, they concluded that

there is inconclusive evidence regarding the efficacy of TEMS for the preservation of muscle mass in ICU patients.

### **2.3.1 Limitations of TEMS**

This ineffectiveness of TEMS is most likely the result of three main limitations. These include the strong discomfort associated with the stimulation<sup>19</sup>, the spatial limitation of muscle fiber<sup>27</sup>, which is typically superficial and partial, as well as the premature decline in evoked force (fatigue) that occurs in a typical training session. These three factors are related to current intensity, which limit the use of TEMS and its effectiveness as a training tool. In the past, several attempts have been made to maximize the electrically intensity, i.e., the main determinant of TEMS effectiveness<sup>28</sup>, and to minimize discomfort and fatigue associated with TEMS, mainly by manipulating current parameters such as pulse waveform<sup>29</sup>, frequency<sup>30</sup> and duration<sup>31</sup>. However, these strategies have provided little evidence of effectiveness.

### **2.3.2 Physiological Considerations of TEMS**

There are a few physiological aspects of TEMS that must be mentioned and considered; in particular the difference in the motor unit recruitment pattern between TEMS and normal voluntary contractions, and the involvement of the nervous system during peripheral TEMS.

The involvement of motor units during a contraction caused by TEMS is considerably different from a voluntary contraction. The first difference is in the recruitment order of motor fibers. In contrast to voluntary contraction, where size-related orderly recruitment

is well documented, the motor recruitment during TEMS is random or not selective, and favors the activation of fast motor units in addition to slow ones with no obvious temporal sequencing, even at low levels of evoked force<sup>32</sup>. With regard to spatial recruitment, a constant intensity of TEMS results in continuous contraction of the same muscle fibers that are close to the stimulating electrodes, and this recruitment decreases as you get farther away from the electrode<sup>33</sup>. However, if current intensity is increased during the training session, new fibers located at a greater distance from the electrode (i.e. deeper) could be activated. Adams et al. (1993)<sup>34</sup> demonstrated a strong linear relationship between muscle CSA that showed contractile activity and torque with TEMS (Figure 4). This figure provides evidence for the limited spatial recruitment of muscle fibers induced by TEMS, or only a limited portion of muscle can be trained by TEMS. The effect of TEMS on neural adaptation is also unique. Hortobagyi and Maffiuletti (2011)<sup>35</sup>, reviewed the neural adaptations during TEMS strength training. They confirmed that early phases of TEMS increased maximal voluntary contraction (MVC) force through neural mechanisms; however, interestingly enough, they found weak evidence to support the involvement of spinal mechanisms to mediate MVC force after TEMS, suggesting MVC strength induced by TEMS training was primarily mediated by supraspinal rather than spinal changes.

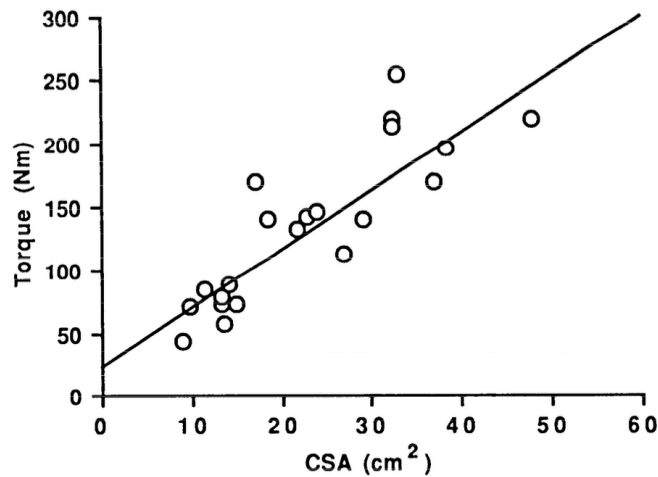


Fig 1. Relationship between stimulated muscle cross-sectional area (CSA) as determined by magnetic resonance imaging (MRI) and torque of m. quadriceps femoris during unilateral isometric actions induced by TEMS).

### 2.3.3 Methodological Considerations of TEMS

There is considerable inter-individual variation in response to TEMS, and the effectiveness of TEMS does not, for the most part, rely on the specific parameters including pulse duration and frequency. It instead relies on subject characteristics. Furthermore, current TEMS parameters are poorly reported and considerably different between studies, and consequently a general lack of homogeneity exists regarding main stimulus parameters for TEMS on human skeletal muscle. Despite incongruence, there are still some suggested guidelines for TEMS electric current parameters. In order to maximize the effectiveness of TEMS, the key is to maximize muscle tension by current frequency and intensity. In order to maximize muscle tension, it is strongly recommended to use pulses of 100-400 $\mu$ s delivered at a stimulation frequency of 50-100 Hz<sup>36</sup>, and at

the highest intensity tolerable<sup>37</sup>. Although few TEMS studies actually measure the force generated during the stimulation, typical TEMS training intensities for healthy quadriceps range from 40-60% of MVC force<sup>38</sup>. Leiber and Kelly<sup>38</sup> measured force generated during TEMS by an ankle strap attached to a strain gauge placed around the subject's distal tibia. By placing three different sets of electrodes over the proximal and distal motor points of the subjects quadriceps femoris muscle, they found an approximate 50% MVC over all subjects and electrodes. As recommended by Muffiulletti et al. 2013<sup>29</sup>, the level of force evoked by TEMS should not necessarily be measured during each training session, because of the linear relationship existing between current intensity and TEMS (Figure 2), force can be predicted by current intensity. However, individual current intensity should be consistently measured.

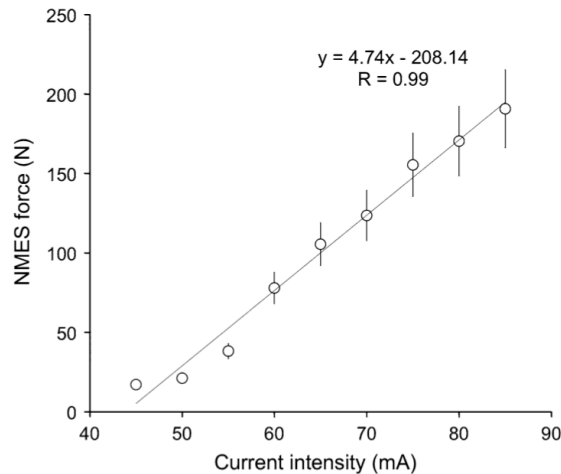


Fig 2. TEMS current intensity is linearly related to TEMS evoked force of the quadriceps muscle. Mean data  $\pm$  standard deviation (N = 10 healthy subjects)<sup>29</sup>.

## **CHAPTER 3: METHODS**

### **3.1 Study Location**

All testing for the study was conducted in the Human Health and Performance Laboratory located in room 119 of the Steel Building at the University of Prince Edward Island, Charlottetown, PEI.

### **3.2 Participants**

Participants were recruited from a population of healthy, young adults between the ages of 18 and 45 yr. Recruitment was primarily done by word of mouth on the University of Prince Edward Island campus and in the surrounding community, between the months of May and August 2014. Both male and female participants were recruited, with the only exclusionary factors being poor health and use of certain drugs/pharmaceuticals known to affect cardiovascular physiology or safe exercise participation.

The participants maintained their habitual amount of physical activity throughout the study which included different levels of activity (1-5 times a week), but none were engaged in any specific training for an athletic event for at least 6 months prior to study. The ethics committee of the University of Prince Edward Island approved this study.

### **3.3 Experimental Protocol**

Upon initial contact via email or phone, all potential participants received a copy of the

study's Informed Consent form (Appendix A) and a Physical Activity Readiness Questionnaire (PAR-Q+) (Appendix B). Volunteers were encouraged to read all forms to ensure that they were still willing and eligible to participate in the study. Interested participants were not required to visit the lab on Day 1 if they found that they were no longer interested or eligible for the study due to the study's exclusion criteria.

Participants signed an Informed Consent form and completed a PAR- Q+ immediately after arriving at the laboratory on Day 1. If participants answered “yes” to any questions on the PAR-Q+ for which they were not subsequently screened back in, or if they met any other exclusion criteria, they were removed from the study. The PAR-Q+ form is a screening method used by health professionals to ensure the client or participant is deemed physically ready to exercise<sup>39</sup>. When the participant was deemed eligible to participate in the study, the testing equipment, protocols, risks, and rationale for the study were then re-explained to them. The participants were encouraged to ask questions, and informed that they may remove themselves from the study at any time.

Each subject came into the laboratory for training four days/week for a total of six weeks. Each training session lasted approximately 30minutes. Each participant was scheduled to train on the same days of the week for each of the six weeks, at around the same time each day. To assess the efficacy of BFR and TEMS training, muscular strength and hypertrophy were measured. Strength and hypertrophy were measured at the beginning of the training (week 0), in the middle (week 3), and at the end (week 6). This timeline is displayed in Figure 3. The detailed study protocol for each phase is described below in section 3.1 *Study Design and Data Collection*.

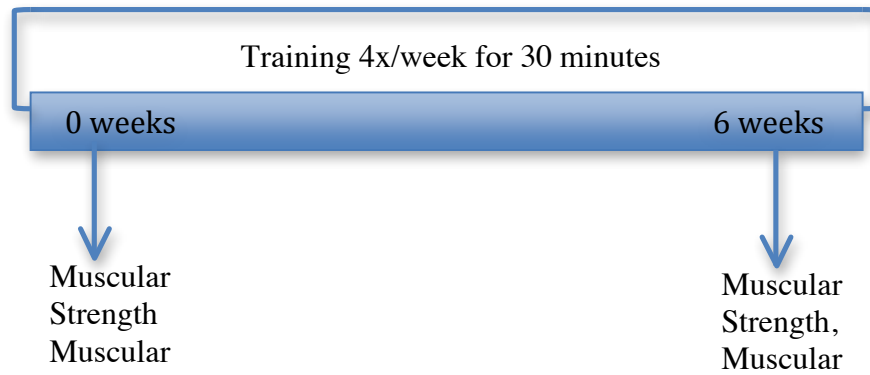


Fig 3: A timeline showing timing of muscular strength and muscular size assessments during the six-week study.

### 3.4 Study Design and Data Collection

There were two distinct parts to this study. We examined the training effects of repeated exposure of TEMS and BFR on both the upper body (part 1), and the lower body (part 2). Subjects concurrently completed both phases. The decision to do simultaneous training of both the upper and lower body was based on the fact that it reduced the number of full body scans (reducing x-ray exposure and cost) required for each participant by 50%.

#### Part 1: Efficacy of BFR and TEMS chronic training (arm)

Both upper and lower appendages of each participant were used. Each subject's dominant and non-dominant arm, determined by asking which arm is used in writing, were randomly designated into two of four possible training groups (one for each arm). The training groups were 1) COMB, 2) TEMS alone, 3) BFR alone, and 4) CON.

Assessments and training were done on the wrist flexor muscle groups of the forearm (the flexor carpi ulnaris, palmaris longus, flexor carpi radialis, and pronator teres, Figure 4).



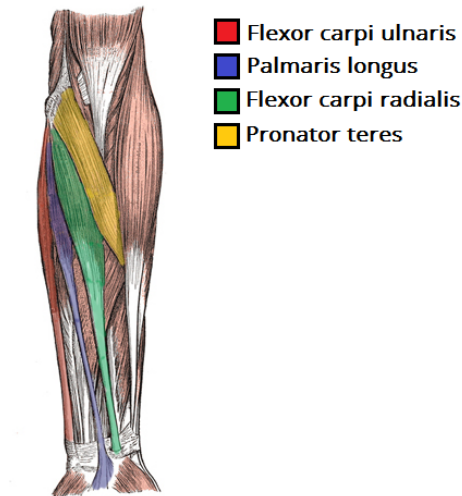


Fig 4. An anatomical image of the leg muscle, highlighting the quadriceps by color.

## Measures

Muscular strength was assessed using a maximum grip strength force (kg). Grip strength was determined using a digitized handgrip dynamometer (Figure 5), connected to a laboratory computer through an iWorx data acquisition system. This system senses an internal pressure rise in the bulb as it is squeezed, causing the sensor to output a voltage proportional to the pressure change. Each participant stood upright and held the dynamometer with their arm fully extended, parallel to the floor. The subject squeezed the hand dynamometer three times, each contraction lasting 3 seconds followed by 3 seconds of relaxation. Each successive contraction was approximately two times stronger than the previous with the third contraction encouraged to be a maximum. It was known that each successive contraction was two times stronger as data were recorded and displayed live on a display window (Figure 6). This test was done twice for each arm with a 1 minute rest given between each test. The greater value for the two trials was

considered as the maximal grip strength value. Each participant was given a familiarization trial before the testing trials. Simultaneous measures of electromyography (EMG- muscle activation, mv) were recorded (using Iworx Labscribe 2 software and data acquisition system) for verification of maximum. The EMG value corresponding to the maximal contraction was noted and used to verify the next maximal contraction. EMG measures were obtained using non-invasive surface electrodes, which detect electrical activity through the skin (similar to an ECG stress test to monitor the heart). One EMG electrode was positioned on the Palmaris Longus and one electrode on the Flexor Carpi Ulnaris. The electrode positions were ones suggested by the Iworx Labscribe program for measuring EMG activity in the forearm flexor muscles. Each participant had the position of the Palmaris Longus electrode recorded by marking its distance (cm) between the humeral medial condyle and the styloid process of the wrist. The Flexor Carpi Ulnaris electrode position was based on position of the first electrode. Previous studies have found moderate to high reliability in handgrip strength test for adolescents<sup>40</sup>. Again, the forearm muscle strength was tested at baseline, 3, and 6 weeks.



Figure 5: A digitized handgrip dynamometer used to measure maximum strength in the forearm muscles.

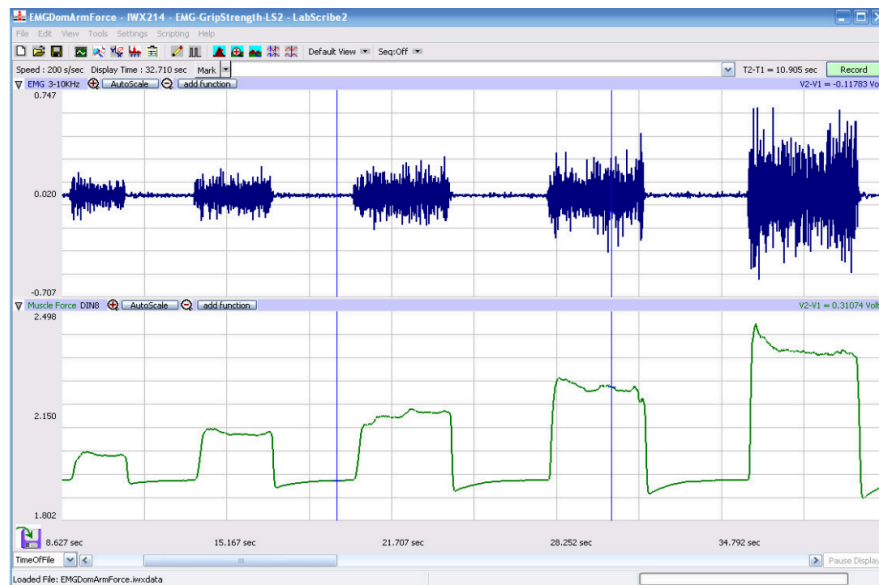


Figure 6. The EMG (upper) and muscle force (lower) for four progressively stronger contractions showed in the display window.

Muscular size was assessed using Dual Energy X-Ray Absorptiometry (DEXA; Figure 7) at the Queen Elizabeth Hospital in Charlottetown, PEI. DEXA is highly reliable to yield body composition estimates of bone material, fat, and lean soft-tissue mass<sup>41</sup>, and is the gold standard of body composition estimates in the exercise physiology field.

Advantages of using DEXA include short scan times, easy set-up of patients for scanning, good measurement precision<sup>42</sup>, and a radiation dose that is very low, at only 10% of a standard chest X-ray<sup>43</sup>. In addition to the reasons previously stated, the biggest advantage of using DEXA in my investigation was for its ability to give specific values for total muscle. This allowed me to accurately assess the change in muscle. Muscle size was tested only at baseline and 6 weeks due to the high cost of DEXA scans.



Fig 7: A Dual Energy X-ray Absorptiometry (DEXA) machine used for total body composition and a segmental breakdown of the amount of fat, muscle, and bone.

### Study Intervention

For training, the BFR intervention was accomplished using an automated tourniquet system (ATS 1500 model; Figure 8) with periodic inflation to 220mmHg (4 min inflation, 4 min deflation intervals<sup>44</sup>). The automated tourniquet system used 4-inch cuffs for the arms, with cotton sleeves also worn under the cuffs to prevent any soft tissue damage. The cuff was positioned at the most proximal part of the arm. The cuff pressure of 220mmHg was chosen to ensure an effective occlusion of blood flow; this was confirmed using near-infrared spectrometry (NIRS), with most individuals reaching 0% SmO<sub>2</sub> within 30 seconds of cuff inflation. NIRS (Figure 9) is a method that provides continuous, non-invasive monitoring of oxygenation in exercising muscles by utilizing the transparency of tissue to photons, to measure changes in the oxygen-dependent absorption changes of these photons by hemoglobin and myoglobin<sup>45</sup>. For the TEMS intervention, stimulation using a **Compex sport mi-runner** (Figure 10) was applied to the wrist flexor muscle groups of the forearm for repeating periods of work and recovery. For the period of work, a pulse train length of 4s was delivered at a stimulation frequency

of 75 Hz<sup>40</sup>. For the period of recovery, a pulse train length of 600s, delivered at a stimulation frequency of 3 Hz. Both periods were at an intensity that was maximally tolerable<sup>41</sup>. The COMB condition will use both modalities simultaneously. The control condition performed no training (only testing). Training took place four times a week<sup>17</sup> for 30 min, for a total of six weeks.



Fig 8. An automated tourniquet device (ATS 1500 model) used for the restriction of blood flow.



Fig 9. Moxy Muscle Oxygen Sensor used to measure variations in muscle oxygenation using the technique of Near Infrared Spectroscopy (NIRS)



Fig 10. A Compex Mi-Runner Sport used to apply electrical muscle stimulation

## **Part 2: Efficacy of BFR and TEMS chronic training (Leg)**

This protocol mirrors the arm protocol above, but assessment and training focused on the quadriceps muscles.

### **Measures**

Muscular strength was assessed using a custom-made isometric limb strength device called a “Leg strength measurement device” (LSMD). The LSMD (patent pending) was developed by Biomedical Engineers at the University of New Brunswick to test isometric strength of the quadriceps muscles. First, participants perform a maximal voluntary isometric contraction by knee extension, in which the LSMD, connected to a laboratory computer through a custom UNB data acquisition and software system, recorded a maximal force (kg). The LSMD was placed on the lower appendage of each subject, locking the subject’s leg into a 45° knee flexion. Once locked in place, the leg cannot be moved or be adjusted. The subject then sat upright in a chair and performed an isometric leg extension against the device. The knee extension was performed three times, each extension lasting 3 seconds followed by 3 seconds of relaxation. Each successive extension was approximately two times stronger than the previous with the third extension encouraged to be a maximum. This test was done twice for each leg with a 1min rest given between each test. The greater value for the two trials was considered as the maximal voluntary contraction. Simultaneous measures of EMG (mv) were recorded for verification of maximum. The EMG value corresponding to the maximal isometric contraction was noted and used to verify the next maximal contraction. Two EMG electrodes were positioned at the center of the palpable Vastus Medialis. This position

was marked by recoding its position (cm) between the top of the iliac crest and the top of the patella by using a tape measure when the lower leg is extended.

Muscular size was assessed using DEXA, as in the arm protocol and was reported as cross sectional area. Muscle size was tested only at baseline and 6 weeks; this was due to the high cost of DEXA scans and participant exposure to x-rays.

### **Study Intervention**

For training, BFR was accomplished in the exact same manner as Part 1 with the occlusion cuff located at the most proximal position on the leg. Stimulation was applied to the quadriceps muscle at a pulse train length of 400 $\mu$ s, delivered at a stimulation frequency of 50-100 Hz, and at the maximally tolerable intensity. The BFR and stimulation condition used both modalities simultaneously. The control condition performed no training (only testing). Training took place four times a week for 30 min, for a total of six weeks.

*Note: Due to the high cost of using the DEXA machine, where possible, each subject was used for both the upper and lower body parts. That is, if possible, each subject had all four limbs (upper and lower appendages) designated to a different training or control group, allowing for quantification of all limbs during a single whole body scan.*



### 3.5 Data Analysis

The differences in muscle strength and size between week 0 and week 6 were found for each arm and leg. These difference scores were grouped according to their intervention and were averaged and presented as means  $\pm$  SD. The intervention groups (TEMS, BFR, COMB, and CON) were compared for any statistical difference using a one-way ANOVA. *Post-hoc* testing was performed by using a Tukey-Kramer test. Statistical significance was set, *a priori*, at  $p < 0.05$ . All calculations were made with SPSS statistical software package v.21.0 (SPSS Inc., Chicago, IL). For transparency, the data was analyzed also by comparing mean differences between the four groups over two time points (pre/post) by using a 2 way repeated measures ANOVA. The F value and P value of the main effects for time (pre/post) and intervention, and their interaction are presented at the bottom of table 2 and 3.

## CHAPTER 4: RESULTS

### 4.1 Participant Characteristics

The study population included 19 participants (10 male, 9 female) aged 18-45 years residing in the province of PEI. Subjects were recreationally active; the physical characteristics of the participants included in the study are shown in Table 1.

Table 1. Physical Characteristics of subjects.

	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )
Overall	24 $\pm$ 6	174 $\pm$ 10	77 $\pm$ 17	23 $\pm$ 3
Range	18-45	158-192	50-109	20-30
Male	22 $\pm$ 2	182 $\pm$ 5	83 $\pm$ 12	25 $\pm$ 2
Female	25 $\pm$ 8	165 $\pm$ 3	57 $\pm$ 5	21 $\pm$ 2

### 4.2 Part 1- Arm Intervention

#### 4.2.1 Maximal Strength

Mean differences in forearm maximal strength between week 0 and 6, for each group are shown in Figure 11. Mean maximal strength for pre and post training is shown for each intervention group in Table 2. After 6 weeks of training, the forearm strength in the COMB group changed by  $3.2 \pm 3.6$ kg, the BFR group by  $2.6 \pm 3.9$ kg; while the TEMS and CON group changed by  $0.7 \pm 3.0$ kg and  $0.6 \pm 2.9$ kg, respectively. There was no significant difference between any groups ( $p=0.2$ ). In addition, there was no significant difference within any group when comparing pre muscular strength and post muscular

strength ( $p>0.1$ ). When analyzing the individualized responses in each group, the BFR and COMB group both had 70% responders ( $>1\text{kg}$  increase), while the TEMS and CON group had 45% and 30% responders, respectively.

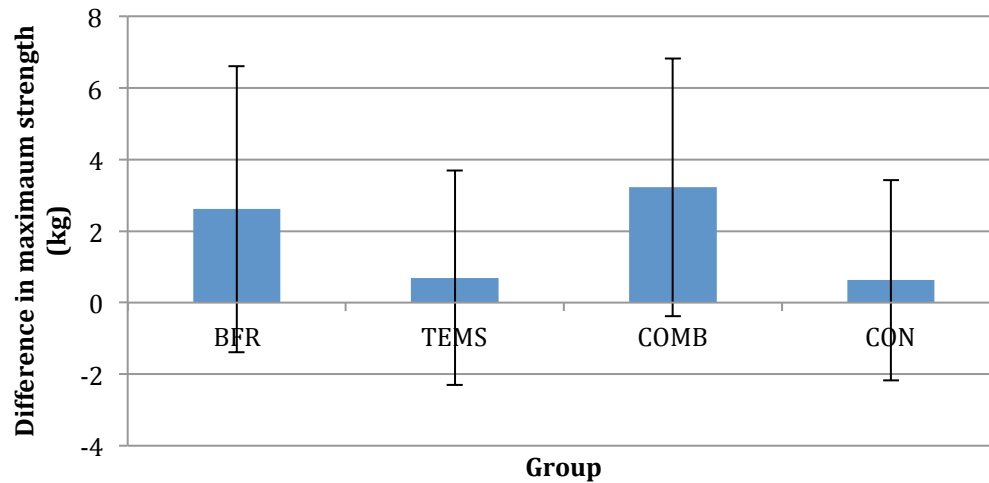


Figure 11. Differences in maximum strength (kg) of the forearm muscle following 6 weeks of stimulation with either transcutaneous electrical muscle stimulation (TEMS) alone, blood flow restriction (BFR) alone, or a combination of the two stimuli (COMB). CON represents the control group who did not receive any stimuli.

#### 4.2.2 Muscle Hypertrophy

Mean differences in forearm muscle size, between week 0 and 6, for each group are shown in Figure 12. Mean muscular hypertrophy for pre and post training is shown for each intervention group in Table 2. After 6 weeks of training, the COMB group changed by  $45 \pm 201\text{g}$ , the BFR group by  $21 \pm 103\text{g}$ ; while the TEMS and CON group changed by  $37 \pm 121\text{g}$  and  $4 \pm 78\text{g}$ , respectively. There was again no significant difference in muscle size between any groups ( $p=0.4$ ). In addition, there was no significant difference within any group when comparing pre muscular size and post muscular size. When analyzing the individualized responses in each group, 60% of the COMB group were responders

(>1g increase), while 40% of the BFR group responded. The TEMS and CON groups both had 30% of individuals respond to the stimuli.

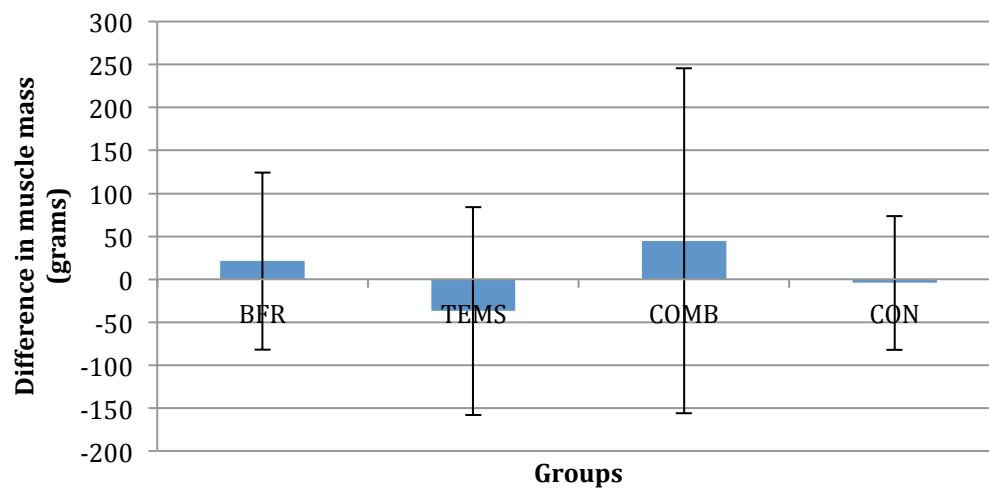


Figure 12. Differences in muscle mass (g) of the forearm flexor muscles, following 6 weeks of stimulation with either electrical muscle stimulation (TEMS) alone, blood flow restriction (BFR) alone, or a combination of the two stimuli (COMB). CON represents the control group who did not receive any stimuli.

Table 2. Mean ( $\pm$ sd) maximum strength (kg) and muscle size (g) of the forearm muscle, pre and post 6 weeks of stimulation with either transcutaneous electrical muscle stimulation (TEMS) alone, blood flow restriction (BFR) alone, or a combination of the two stimuli (COMB). CON represents the control group who did not receive any stimuli (N=19,  $p > 0.05$  Pre versus Post). Mean differences between the four groups were also compared over two time points (pre/post) by a 2 way repeated measures ANOVA. The F value and P value for the main effects of Time and Intervention (Intvn) and their interaction (Sphericity assumed) are presented and italicized at the bottom of the table.

	<b>Maximal Strength (kg)</b>		<b>Muscle Hypertrophy (g)</b>	
	<b>Pre</b>	<b>Post</b>	<b>Pre</b>	<b>Post</b>
<b>BFR</b>				
Total	<b>31.0 (<math>\pm 7.1</math>)</b>	<b>33.6(<math>\pm 6.9</math>)</b>	<b>3154(<math>\pm 1046</math>)</b>	<b>3308(<math>\pm 1163</math>)</b>
Males	35.4( $\pm 5.8$ )	37.9( $\pm 4.9$ )	3772( $\pm 913$ )	3976( $\pm 960$ )
Females	24.4( $\pm 1.2$ )	27.1( $\pm 3.4$ )	2227( $\pm 229$ )	2194( $\pm 290$ )
<b>TEMS</b>				
Total	<b>30.4 (<math>\pm 7.4</math>)</b>	<b>31.0(<math>\pm 6.1</math>)</b>	<b>3193(<math>\pm 1152</math>)</b>	<b>3156(<math>\pm 1154</math>)</b>
Males	35.5 ( $\pm 5.4$ )	35.7( $\pm 3.8$ )	4109( $\pm 664$ )	4082( $\pm 647$ )
Females	23.9( $\pm 3.4$ )	25.2( $\pm 2.2$ )	2048( $\pm 273$ )	1999( $\pm 260$ )
<b>COMB</b>				
Total	<b>30.2(<math>\pm 6.4</math>)</b>	<b>33.5(<math>\pm 6.2</math>)</b>	<b>3314(<math>\pm 1109</math>)</b>	<b>3358(<math>\pm 1199</math>)</b>
Males	33.5 ( $\pm 4.8$ )	37.5( $\pm 4.2$ )	3985( $\pm 958$ )	4056( $\pm 1085$ )
Females	25.5 ( $\pm 6.0$ )	27.4( $\pm 4.4$ )	2308( $\pm 112$ )	2313( $\pm 103$ )
<b>CON</b>				
Total	<b>29.2(<math>\pm 10</math>)</b>	<b>30.9(<math>\pm 8.2</math>)</b>	<b>2646(<math>\pm 1118</math>)</b>	<b>2642(<math>\pm 1162</math>)</b>
Males	43.2( $\pm 3.4$ )	41.9( $\pm 0.5$ )	4182( $\pm 381$ )	4251( $\pm 331$ )
Females	22.8( $\pm 2.8$ )	25.4( $\pm 3.1$ )	1878( $\pm 185$ )	1838( $\pm 172$ )
<i>Time Effect</i>	<i>F=0.7</i>	<i>P=0.5</i>	<i>F=0.1</i>	<i>P=0.8</i>
<i>Intvn Effect</i>	<i>F=8.7</i>	<i>P=0.2</i>	<i>F=0.2</i>	<i>P=0.1</i>
<i>Interaction</i>	<i>F=1.1</i>	<i>P=0.4</i>	<i>F=2.2</i>	<i>P=0.3</i>

## **4.3 Part 2- Leg Intervention**

### **4.3.1 Maximal Strength**

Mean differences in quadriceps muscle strength, between week 0 and 6, for each group are shown in Figure 13. Maximal strength for pre and post training is shown for each intervention group in Table 3. The One-way ANOVA produced an F value of 3.5 and a p-value of 0.03. Post-hoc analysis revealed only a significant difference between the COMB group and CON ( $p=0.02$ ). The COMB group saw a change in mean isometric leg strength of  $32 \pm 19\text{kg}$  between week 0 and week 6, while the CON group saw a mean isometric leg strength change of  $3 \pm 11\text{kg}$ . Mean strength of the BFR and TEMS groups changed by  $16 \pm 28\text{kg}$  and  $18 \pm 17\text{kg}$ , respectively. The BFR and TEMS groups were not significantly different from each other, or any other group. In addition, there was no significant difference within any group when comparing pre muscular strength and post muscular strength. When analyzing the individualized responses in each group, the BFR and TEMS group both had 100% responders ( $>1\text{kg}$  increase), while the BFR and CON group had 60% and 30% responders, respectively.

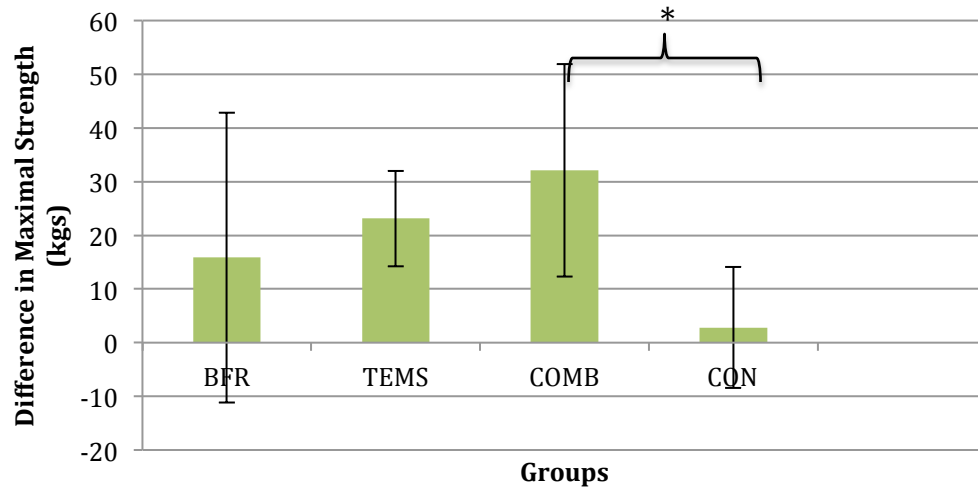


Figure 13. Differences in maximum strength (kg) of the quadriceps muscle, following 6 weeks of stimulation with either transcutaneous electrical muscle stimulation (TEMS) alone, blood flow restriction (BFR) alone, or a combination of the two stimuli (COMB). CON represents the control group who did not receive any stimuli. \* Indicates significant difference. Error bars represent standard deviation.

### Muscle Hypertrophy

Mean differences in quadriceps muscle size, between week 0 and 6, for each group are shown in Figure 14. Muscular hypertrophy for pre and post training is shown for each intervention group in Table 3. After 6 weeks of training, the COMB group changed by  $95 \pm 258\text{g}$ , and the BFR group by  $70 \pm 387\text{g}$ , while the TEMS and CON group changed by  $79 \pm 439\text{g}$  and  $-83 \pm 279\text{g}$ , respectively. There was no significant difference in leg muscle size between any group ( $p=0.73$ ). In addition, there was no significant difference within any group when comparing pre muscular size and post muscular size. When analyzing the individualized responses in each group, 70% of the COMB group were responders ( $>1\text{g}$  increase), while 60% of the TEMS group responded. The BFR and CON group had 30% and 20% of participants respond, respectively.

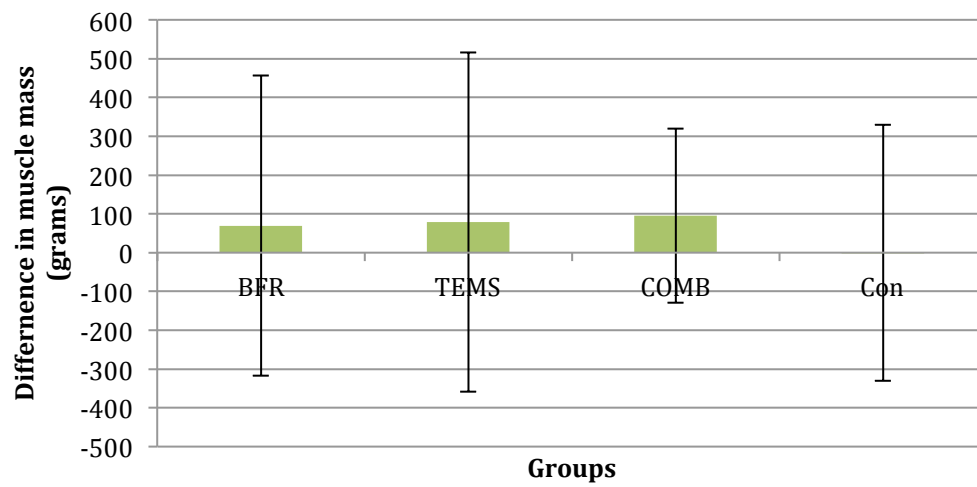


Figure 14. Differences in muscle mass (g) of the quadriceps muscle, following 6 weeks of stimulation with either transcutaneous electrical muscle stimulation (TEMS) alone, blood flow restriction (BFR) alone, or a combination of the two stimuli (COMB). CON represents the control group who did not receive any stimuli.



Table 3. Mean ( $\pm$ sd) maximum strength (kg) and muscle size (g) of the quadriceps muscle, pre and post 6 weeks of stimulation with either electrical muscle stimulation (TEMS) alone, blood flow restriction (BFR) alone, or a combination of the two stimuli (COMB). CON represents the control group who did not receive any stimuli. (N=19,  $p > 0.05$  Pre versus Post). Mean differences between the four groups were also compared over two time points (pre/post) by a 2 way repeated measures ANOVA. The F value and P value for the main effects of Time (t) and Intervention (Intvn) and their interaction (Sphericity assumed) are presented and italicized at the bottom of the table.

	<b>Maximal Strength (kg)</b>		<b>Muscle Hypertrophy (g)</b>	
	<b>Pre</b>	<b>Post</b>	<b>Pre</b>	<b>Post</b>
<b>BFR</b>				
Total	<b>167(<math>\pm</math>46)</b>	<b>183(<math>\pm</math>50)</b>	<b>9313(<math>\pm</math>2310)</b>	<b>9418(<math>\pm</math>2300)</b>
Males	194( $\pm$ 27)	206( $\pm$ 31)	11045( $\pm$ 1017)	11169( $\pm$ 855)
Females	126( $\pm$ 37)	142( $\pm$ 49)	6716( $\pm$ 734)	6790( $\pm$ 790)
<b>TEMS</b>				
Total	<b>141(<math>\pm</math>44)</b>	<b>159(<math>\pm</math>43)</b>	<b>9311(<math>\pm</math>2551)</b>	<b>9391(<math>\pm</math>2427)</b>
Males	175( $\pm$ 30)	187( $\pm$ 18)	11339( $\pm$ 1943)	11435( $\pm$ 1518)
Females	107( $\pm$ 26)	132( $\pm$ 32)	7283( $\pm$ 1009)	7345( $\pm$ 1054)
<b>COMB</b>				
Total	<b>136(<math>\pm</math>38)</b>	<b>168(<math>\pm</math>53)</b>	<b>9139(<math>\pm</math>2284)</b>	<b>9234(<math>\pm</math>2256)</b>
Males	159( $\pm$ 28)	201( $\pm$ 41)	10562( $\pm$ 1584)	10630( $\pm$ 1468)
Females	103( $\pm$ 20)	117( $\pm$ 22)	7004( $\pm$ 1301)	7139( $\pm$ 1476)
<b>CON</b>				
Total	<b>127(<math>\pm</math>38)</b>	<b>122(<math>\pm</math>29)</b>	<b>7385(<math>\pm</math>1840)</b>	<b>7384(<math>\pm</math>1738)</b>
Males	153( $\pm$ 34)	142( $\pm$ 34)	10089( $\pm$ 1036)	9956( $\pm$ 1108)
Females	111( $\pm$ 26)	110( $\pm$ 12)	6304( $\pm$ 467)	6356( $\pm$ 196)
<i>Time Effect</i>	<i>F=14.8</i>	<i>P=0.004</i>	<i>F=0.7</i>	<i>P=0.4</i>
<i>Intvn Effect</i>	<i>F=2.4</i>	<i>P=0.09</i>	<i>F=4.9</i>	<i>P=0.07</i>
<i>Interaction</i>	<i>F=4.8</i>	<i>P=0.008</i>	<i>F=0.7</i>	<i>P=0.6</i>

## **CHAPTER 5: Discussion**

The aim of this study was to examine the effect of combining blood flow restriction with a low intensity transcutaneous electrical stimulus. Two parts were completed in attempt to answer this research question. The first part examined the effects of repeated exposure of TEMS and BFR for six weeks on the musculature of the forearm, while the second part examined the effects in the musculature of the anterior upper leg. In order to assess the efficacy of repeated exposure of TEMS and BFR, the changes in muscular strength and size were measured following six weeks of regular application of this stimuli, or a variant of each of its components. The percentage of participants that responded to the stimuli, or each of its components was also presented, which are important values due to the strong possibility of physiological responders and non-responders present in my sample, as discussed below. The forearm and upper leg were selected areas as each represent different types of muscles with different functions that could elicit different effects. For instance, there is a difference in the predominant fiber type between these two muscles, as the anterior upper leg has increased slow twitch fibers, due to its role in posture and locomotion, while the forearm has increased fast twitch fibers due to its fine motor movements. These differences in muscle types could influence differential outcomes.

This investigation is unique as it is the only study, to my knowledge, that looks at combining the stimulus of BFR with the stimulus of TEMS. This thesis provided some interesting findings, which adds to the literature as the only study to apply this novel

intervention, which could have practical implications. Based on the results, inferences and speculations can be made and are discussed below.

## **5.1 Arms**

As seen above, there were no statistical differences between or within any groups, suggesting no superior effect of any of the interventions. With acknowledgement of no significant differences between or within any of the groups, the following interpretation must be taken with caution and does not imply definite changes, only supposition and observation. The changes in maximal strength and muscle hypertrophy both demonstrate the COMB group and BFR manifesting the largest change in forearm strength and size after 6 weeks; with the COMB group changing the most. Only small changes occurred in the TEMS and CON group for both strength and size. These group means seem to follow a very promising pattern that could establish proof of concept for this methodology.

Furthermore, when noting the percent responders in each group, it seems the COMB and BFR group has the highest percent of individuals that responded to the stimulus.

However, there is an obvious lack of significance that most likely relates to the high inter-individual variability within each group. There is value in noting the individualized response among participants in my sample, as it is plausible that there are some individuals that are physiological responders to the stimulus, while others were not. This responder vs. non-responder concept is a well-recognized phenomenon in physiological/genetic research that is gaining significant support in the applied sciences. The individuality in response may not suggest that the intervention is not effective

overall, but rather that the intervention may be of varying effectiveness for differing groups of people, for which the defining grouping variable has yet to be uncovered.

There are numerous examples in the literature where this occurs when dealing with restriction of blood flow to the tissues. Firstly, Hopman et al <sup>49</sup> investigated short bouts of BFR and subsequent reperfusion to improve maximal performance in recreational individuals <sup>46</sup>. Her team found that subjects who underwent these short bouts before an exercise trial resulted in gains of both maximal power (1.6%) and peak oxygen consumption (3%). However, despite an overall increase there were some subjects that were obvious non-responders and negative responders to the stimulus. St Michel et al <sup>47</sup> also demonstrated similar variation with continued research on this technique using time trial performance of elite athletes <sup>44</sup>. National level swimmers performed a maximal effort 100m-time trial twice, once with a sham control and a second time immediately following short bouts of BFR and reperfusion. They observed a mean increase of 0.7s in swim time but the individualized response to the stimulus, as seen in Figure 16, was varied

This concept of responders vs. non-responders is also a logical and plausible explanation for the high variability in the data. A difference in response to the stimulus would lead to some individuals increasing muscle size and strength, while others not, resulting in a variation of the change in muscle size and strength over the six weeks. To further explore this possibility, the data were re-plotted and is presented in Figure 15. As seen in Figure 18, there are some individuals that had an increase in maximum strength over six weeks

(blue lines), while maximum strength in others decreased (red lines) or stayed the same (black lines). It is plausible that our sample experienced this variation in responsiveness, as supported by the large inter-individual variability of the change in muscle size. This variable was measured using a DEXA scan, which is an objective and precise measure, and therefore, the variation is unlikely to be explained by human or measurement error.

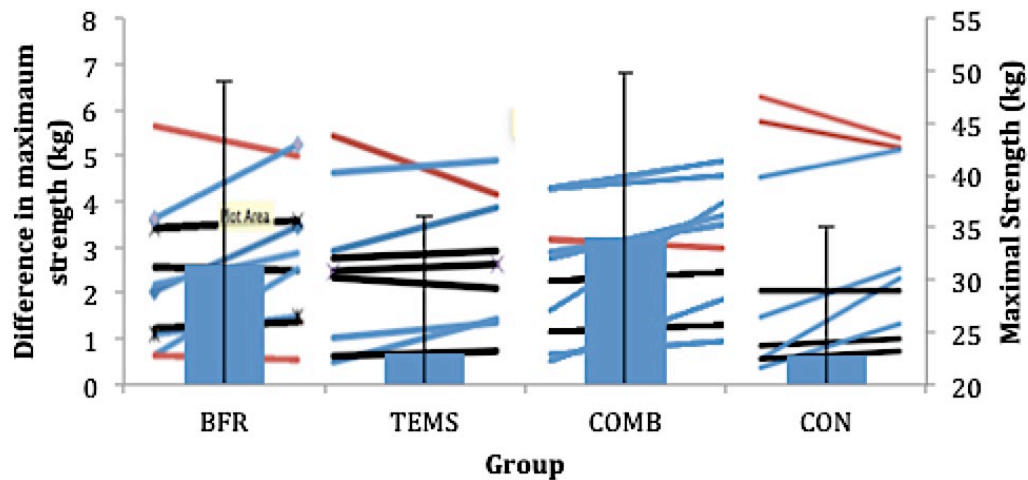


Fig 15. Differences in forearm maximum strength (kg) between week 0 and week 6 for each group (bars). Individual responses are depicted by colored line graphs. Each line represents a different forearm. A blue line graph represents an increase in maximal strength ( $>1\text{kg}$ ), a red line graph represents a decrease in maximal strength ( $>1\text{kg}$ ), while a black line graph represents no change.

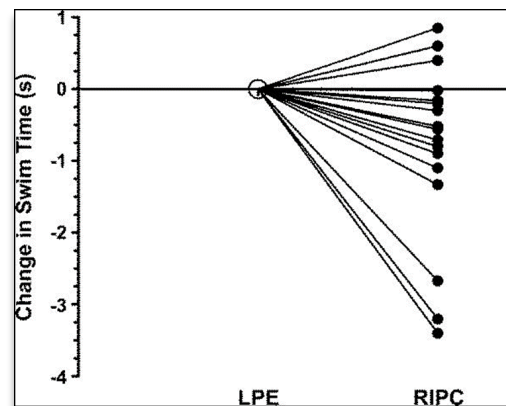


Figure 16: The effect of short bouts of BFR and ischemia on maximal swim time expressed as absolute difference (s) from low-pressure experimental intervention, irrespective of treatment order. Values are expressed in seconds. Each black line represents different elite swimmers.  $n = 18$  for all groups.

Another reason for the high inter-individual variability may be due to the disparity in participant's baseline muscle strength and size. Some individuals had very strong, large muscles at onset, while other individuals did not. Subjects with weaker, smaller muscles are more likely to experience a greater change than the subjects whom had stronger, larger arms owing to a baseline effect. This would result in muscle size and strength differences after six weeks to be varied. It is common in traditional exercise training studies that a similar relative load could represent a different absolute load amongst subjects of differing size and strength. In the current study, a given absolute exercise stimulation may have differentially penetrated and affected smaller vs larger musculature. It is possible that the observation of responders and non-responder in the current data is not due to a physiological difference in response rather the disparity if a subject's baseline strength and size. A high baseline strength and size could result in a non-response due to a decreased likelihood in experiencing a change, and a low baseline strength and size could result in a response due to an increased likelihood to experience a change. When considering the difference in baseline size and strength between male and females, it is obvious that females most often had weaker and smaller arms at baseline, and males had larger stronger arms at baseline; more often the larger increase is observed in the females. Therefore, this increased variability and response due to baseline strength and size is most likely due to both males and females being part of the study sample.

Another explanation of the large variability may be the change in activity level during the six weeks. We instructed every participant to continue his or her normal training routine, and to not increase or decrease his or her training duration or volume. Notwithstanding

intentional training changes, it is still possible that an individual altered their habitual level of activity during the six weeks of training, even if unintentional, which consequently would lead to alteration in muscle size and strength not prompted by the intervention. As mentioned previously, data collection started for this project in May and continued until the end of September. As the weather became warmer and more pleasant, participants may have been more likely to increase their level of activity, simply by doing more walking, swimming, or cycling. As school started in September, participants training during this time may have decreased their level of activity by result of less free time. Others may have started playing a recreational sport, while others may have stopped. There are a lot of reasons that could have resulted in either an increase or decrease in level of activity, which in turn could have affected the variation in muscle size and strength change. This is plausible as the large variation occurred in every group. A physical activity log should have been employed to better see if these theoretical effects influenced my results. These reasons presented above along with the fact that there were only 8-10 individuals per group, another potential explanation of the large variation, and are deserving of follow-up. Upon doing an *a priori* power calculation (80%) of the total participant number needed to reach statistical significance between the COMB and CON group with the effect size observed in our data is 48.

There is a possibility that the magnitude of response was related to the pain threshold or intensity tolerated from the TEMS by each individual. The TEMS intensity parameter was predetermined to be maximally tolerable, meaning that the intensity of the stimulation for each individual was just below that individual's pain threshold. As the

muscle adapted to the stimulus, the participant was encouraged to increase the stimulus to that pain threshold. This pain threshold is different for each individual and it is possible that the magnitude of effect was related to how much an individual increased the electrical intensity.

## **5.2 Legs**

There was a lack of statistically significant differences between or within any groups regarding hypertrophic changes, suggesting no differential effect of the intervention. Despite this, it is possible that an effect is masked by the relatively large variance in the data. The reasons for the large variation can be explained by the same reasons outlined in part1. It is worth reminding the reader that the author understands that there is no definite change in groups, and the following interpretation is based on speculation of group means. The group means again follow a promising pattern. It seems from the group means that muscle hypertrophy was realized after 6 weeks for the COMB, TEMS, and BFR groups, with the COMB group increasing the most; while changes in the CON group were minimal. Furthermore, the COMB group had the highest percentage of individuals that responded to the stimulus.

Maximal strength seems to follow a similar pattern as muscle hypertrophy as there seems to be an increase after 6 weeks for the COMB, TEMS, and BFR groups, with the COMB group increasing the most, but a minimal change in the CON group. Inter-individual variability was again observed in these groups, yet there was a significant difference between the COMB group and the CON group, providing evidence for our hypothesis that the COMB group will have the greatest effect on muscular adaptations.



The noteworthy observation in part 2 is the change of all groups, except the CON group. A plausible explanation for this is a phenomenon called the cross-transfer effect<sup>47</sup>, where the intervention for one side of the legs could have caused an increase in muscle size and strength in the opposite leg. It is well described in the literature that resistance training with one limb can cause a concomitant increase in muscular strength in the contralateral, untrained limb<sup>48</sup>. This cross transfer effect may be explained by acute post exercise changes in systemic plasma testosterone and growth hormone, as it has been demonstrated that endogenous, as well as exogenous testosterone plays an important role in muscular hypertrophy<sup>49</sup>. Moreover, it has been shown that acute changes in plasma concentration of growth hormone after an exercise session are positively correlated with the extent of muscular hypertrophy after the period of exercise training<sup>49</sup>.

Takarada<sup>50</sup> et al. have demonstrated that low-intensity occlusive exercise for lower extremities caused a larger increase in plasma concentration of growth hormone than did normal exercise of same intensity and volume. Therefore, if there are increases in the systemic concentrations of anabolic hormones during resistance training with BFR, and these hormones promote muscular hypertrophy, resistance training with BFR for a given muscle cannot only be expected to induce muscular hypertrophy in the same muscle but also in other muscle trained without blood flow restriction. Madarame et al.<sup>51</sup> investigated this possibility of whether cross-transfer of muscle hypertrophy occurs, specifically if leg resistance exercise combined with BFR had an effect on arm muscle that were either untrained or normally trained at low intensity. Their main finding was that there was only an increase in arm muscle size and strength when trained arm muscles

were combined with leg muscles undergoing resistance exercise with BFR, and not when combined with leg muscles undergoing resistance training without BFR. This suggests that exercise intensity used for arm muscles was not sufficient for promoting muscular adaptation, but a combination of the leg exercise stimulus and factors associated with BFR cause muscular adaptation, upholding the cross-transfer effect theory.

To analyze our data for this concept of BFR triggered systemic factors being associated with muscular adaptations in other appendages, I performed a *post-hoc* responder analysis; a consideration of a BFR associated (BFR alone or COMB) or non-BFR associated (TEMS or CON) lower appendage and the differences that occurred in this appendage when the opposite lower appendage undertook different interventions.

Individuals that had a lower appendage designated to a BFR associated group (BFR alone or COMB) matched with the other leg also designated to a BFR associated group were not significantly different from individuals who had a BFR leg matched with a non-BFR leg when considering the change of muscle mass ( $p=0.2$ ) or strength ( $p=0.3$ ). Even when comparing means there is no indication of a cross-transfer effect, as there was only an increase of 28g and 17 kg ( $n=6$ ) in the outcome leg that was combined with another BFR type leg compared to 160g and 24 kg ( $n=10$ ) increase in the outcome leg when combined with a non-BFR group.

Owing to the cross transfer effect, it is possible that there could be a further increase in muscle size and strength as the total number of BFR associated interventions designated to a subject increases. Every participant had at least one BFR associated appendage (upper or lower) in addition to an outcome BFR associated designated lower appendage. When statistically comparing the change in muscle size and strength in the outcome BFR

associated lower appendage when combined with 1 (n=8) or 2 (n=8) other BFR type appendages in the same subject, significant differences in maximal strength ( $p=0.7$ ) or size ( $p=0.1$ ) were not apparent. This null finding occurred despite the mean change in muscle size (136g) and strength (26kg) being higher when combined with 2 other BFR type appendages compared to just 1 other (109g and 16kg). This post hoc analysis provided no statistical evidence to suggest the cross-transfer effect occurring in our study, but it is important to note that this was not a planned comparison and was relatively underpowered. As such, the notion that such an effect did not occur cannot be conclusively stated, as it is possible that, again, the relatively large variation in the data is masking the effect in a similar fashion to the problem that was met in the original analysis.

Madarambe et al.<sup>54</sup> also observed no muscular adaptations in untrained arm muscles that were combined with leg muscles undergoing resistance exercise with BFR. This may suggest that any systemic hormone or factors released from BFR must be combined with a localized exercise stimulus to produce muscular adaptations. This may be a partial explanation for the observed increase in all groups but the control group, as there needs to be an induced exercise stimulus in order to instigate adaptation.

Another explanation of no increase in the CON group may be due to the specific randomization of my groups. The randomization of upper and lower appendages occurred separately. Each arm (and leg) of every subject was randomized into 1 of 4 possible training groups in an effort to maximize subject efficiency (training time) and minimize the costs and subject exposure to x-rays during DEXA scanning. However, appendage randomization to study arms was done in a way that equally matched each intervention

with a control arm. For instance, the number of BFR interventions legs matched with a control leg equaled the number of TEMS, COMB, and CON legs matched with a control arm. This was done to wash out any bias on the control arm from one specific group and any contralateral effect. However, other contralateral effects may have occurred, as we did not match each group equally to every other group. By not diminishing the reasons above, the main reason for the lack of change in the lower appendage control group was due to the addition of full control subjects. Due to one individual that did not complete the study and the method of randomization, there was a lack of lower appendages designated into the control group. In order to supplement this group, the recruitment of two additional individuals occurred for this study. Both lower appendages of these individuals were included in the control group and did not undergo training in any other appendage (full control). Since these subjects were not undergoing training, the cross-transfer effect was not present and there was very minimal change in these four appendages. This influenced the over-all mean of the lower appendage control group, resulting in a lack of change in the aforementioned group.

This cross-transfer effect could be another possible explanation for the high variability. Due to each limb of each subject being randomized into an intervention group, subjects had different combinations of interventions applied to their limbs. Depending on certain intervention combinations, one individual could have experienced more of a contralateral effect than another resulting in the possibility of, despite having the same intervention on the same limb, could have experienced more of an increase in strength and size in that limb due to paired interventions.

### **5.3 Strengths, Limitations, and Assumptions**

The main strength of this project is its innovation and potential. To my knowledge this is the first study investigating the combination of TEMS with BFR. This is a technique that could improve the effectiveness of TEMS, and a practice that could lead to the maintenance and improvement of skeletal muscle in sarcopenic susceptible populations. This could be a key study in the process of achieving this goal.

Another strength of this study was that this technique was successfully performed in healthy individuals without physical impairment. Previous literature has validated the safety of the BFR training technique; however, the potential negative effects associated with the prolonged application of a combination of BFR with TEMS were unknown. None of my participants experienced any chronic soreness, fatigue, or any other negative effects.

Due to the strong possibility of the cross-transfer effect, it was limiting to employ more than one intervention on each individual. This made it difficult to know exactly which intervention was causing the adaptive effect, and could have increased the intra-individual variability (as explained above). In future research it would be best to apply only one intervention for each individual. Each limb of the individual could still be used to cut down on recruitment but make it the same intervention in order to allow the researcher to observe the contribution of each intervention separately on the muscular adaptations.

Another limitation was an imprecision in the control of the activity level of the participants. Despite asking participants to maintain their current training volume and

duration, recreational activity level of participants could have changed during the six weeks of training. This could have introduced changes in the musculature that was not due to the intervention. In future investigations I will design my study around a population that has a very similar and consistent activity level throughout the duration of my study.

The nature of this intervention, specifically the obvious visual differences in interventions, did not allow for a true blinding, nor double blinding, of participants and researchers. Despite not revealing to the subjects what intervention group I expected to cause the greatest adaptations, individuals could have considered or believed one group to be superior to another leading to a possible placebo response. Use of a sham control (i.e. cuff inflated to 10mmHg) in future research may be of some value.

Finally, the handgrip strength test used in this study to test maximal strength of the wrist flexors of the forearm, also tests the strength of the Flexor digitorum superficialis, which was not a targeted muscle in electrical stimulation or EMG recording. This could explain no observed effect in the arm protocol.

#### **5.4 Conclusion & Future Directions**

There was no observed change of the forearm, in strength or size, when combining BFR with TEMS when comparing it to the CON group. This is mainly due to the high inter-individual variability and differential adaptive responses. However, there was a change in leg strength when combining BFR with TEMS when comparing it to the control group. This is an important finding as this provides indication that this technique succeeds in

increasing muscle strength. Although, it is not known which component, or whether it is the combination of the components, is causing the strength increase. This is a very novel and exciting concept that has much potential in areas of performance, recovery, and rehabilitation. Much more research needs to be performed, but this study provides a good stepping-off point for further research.

As mentioned above, in future work there needs to be more control of the cross-transfer effect, with one individual only designated to one intervention group in order to separate the degree of adaptation each intervention contributes to muscle strength and size.

Second, more research is needed to determine if there is an increased muscular adaptation caused by the stimulus of BFR combined with TEMS. We have preliminary evidence to suggest it very well may, but there was too much variability to reach statistical significance. Future studies need to concentrate on reducing the variability. This could be done using samples of immobilized individuals or elite athletes whose respected population has a very standardized activity level. These homogeneous samples would also allow for a similar baseline strength and size, reducing the percent change variability. An additional way to reduce the variability is to consider a different study design that uses repeated tests on the same subject (cross-over design); this would limit responder variability.

Finally, the concept of responder vs. non-responder needs to be further investigated. If strong evidence can be acquired, then this technique's application potential is still present but only in certain situations. For instance, if individuals either physiologically respond to the stimuli or physiologically do not, then on a population health level, this stimuli would not be very relevant as it will not improve the overall health of a group of individuals.

However, if one is looking at this technique on an individual level, this technique could be very important. A health professional or an elite athletic coach could recognize a physiological responder and use this technique on these individuals, while finding a different practice that could benefit the non-responders. This would still present great benefits to many people.



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# APPENDIX A: STUDY INFORMED CONSENT FORM

## CONSENT FORM

**Title of Project:** The physiological effects of blood flow restricted muscle stimulation  
Arm / leg trial

**Investigators:** Jamie Burr, PhD (Principal Investigator)  
Josh Slys

**Institutions:** Applied Human Sciences, the University of PEI

**Contact Person:** Dr. Jamie Burr, Email: [jburr@upei.ca](mailto:jburr@upei.ca), Tel: 902-620-5225

We are interested in evaluating the effects of muscular stimulation when blood flow to that muscle is temporarily reduced. Emerging evidence suggests that low load exercise stimuli (i.e. <25% maximal capacity) can lead to significant muscular adaptations when blood flow to a muscle is restricted or occluded. To date, research has primarily focused on exercise using light weights or aerobic-type exercise such as treadmill walking. Electrical muscle stimulation has been used for a number of years in rehabilitative settings, but muscular adaptation as a result of stimulation is limited owing to the discomfort caused by the high intensity stimulus necessary to cause greater adaptation. Combining a low intensity electrical stimulus with blood flow restriction offers the potential to stimulate substantial muscular adaptation without undue discomfort. A future potential application of this research would be to design automated commercially available devices which appropriately stimulate muscles to promote training adaptations for users in both good health and disease.

### Procedures:

If you are interested in participating in this investigation please complete and sign the consent form.

***Before initiating any physical testing or training, you will be required to complete a Physical Activity Readiness Questionnaire (PAR-Q+) to evaluate your ability to safely complete the proposed testing. Should any areas of concern regarding your current health/risk factors for exercise be identified, you will not be allowed to participate until you have received clearance from your doctor. Please tell the research team if you are currently taking any medication for cardiovascular disease or diabetes (examples include medications for : high blood pressure, "water pills", diuretics, beta blockers, ACE inhibitors, cholesterol medication, metformin, insulin or other diabetes related meds.)***

All research will be conducted at UPEI within the Steel Building, which houses the UPEI Human Performance and Health Laboratory.

**For testing days we ask that you arrive at the laboratory having refrained from a heavy meal, caffeine, or nicotine (within 3 hr) or consumption of alcohol (12hrs). We further ask you to refrain from a heavy work-out for at least 24 hr preceding all testing.**

**Part 1:**

Each limb (arm and leg) will be assigned to a group for strength testing, training and then re-testing following a period of 6 weeks. During the training period, you will be asked to participate 4 days/wk in a repeated stimulation of both your arm and leg muscles using one of 4 combinations of training stimulus. Each of your arms/legs will be given a different condition for training from the following 1) muscle stimulation only, 2) blood flow restriction only, 3) both muscle stimulation and blood flow restriction or 4) nothing at all. The blood flow restriction will be applied using a standard blood pressure cuff (just like those used in a doctor's office), with a periodic inflation ( 4 min on, 4 min off), of 220mmHg . You will be able to control the intensity of you muscle stimulated muscle contractions, based on your own comfort level. Each training session (both arms/legs) will take a total of approximately 30-40 min.

**Testing procedures:**

*Arm group-* Measures: will be completed using the flexor muscle groups (those used to make a fist) of your forearm. Your muscular strength and muscular endurance will be determined using a digitized handgrip dynamometer, which senses your grip pressure. While you maximally squeeze the dynamometer measures of your muscle activity (EMG) will be recorded from the surface of your skin using non-invasive skin electrodes, which detect electrical activity through the skin. This measure will occur before training, and will be repeated during a number of training sessions throughout (3 wk, and 6wk). Your muscular size will be determined using Dual Energy X-ray Absorptiometry (DEXA). A DEXA scan, which is done at the Queen Elizabeth Hospital in Charlottetown, takes estimates of body composition, which will give us accurate values for muscle size. These measures will occur before training, and after training.

*Leg group-* Measures: will be completed using the large muscles of your leg, i.e. your thigh muscles (quadriceps). Strength will be measured a traditional muscle maximal leg extension using a isometric leg strength device. Muscle activation will be measured similar to the "arm group" using EMG recorded from the surface of your skin above the contracting muscle group. This measure will occur before training, and will be repeated during a number of training sessions throughout (3 wk, and 6wk). Muscle Size will be determined using a DEXA scan, as in the "arm group." These measures will occur before training, and after training.

**Total participation time for this study is estimated at 18-20 hrs.**

**Risks:**

The test of muscle strength will be of a short duration, and will cause little to no discomfort. Similarly, the physical stress of low intensity muscle stimulation is not expected to cause large noticeable exercise effects (i.e. you will not be breathing hard, or sweating like you would expect while jogging or cycling). There are no permanent known adverse side effects that are due to these types of exercise sessions. Electrical muscle stimulation can cause your skin to become irritated, in which case removal of the electrodes and discontinuation of the stimulation should make the irritation stop. Occasionally a very strong muscle contraction can be momentarily uncomfortable, but will not cause any serious pain or damage. Blood flow restriction has been shown to be safe and is commonly employed as a training methodology in other parts of the world. Persons with known vascular disease, or diabetes might be at a higher risk of rupturing an unstable vascular plaque, and should not participate as this could lead to an adverse cardiovascular event. The DEXA scan emits off low level of radiation however is safe, as it gives off less radiation than a standard chest X-ray. All exercise testing and body composition

measures will be performed under the supervision of trained personnel including a certified exercise physiologist (Canadian Society of Exercise Physiology (CSEP)). A CSEP-Certified Exercise Physiologist is a university-trained individual that has obtained the most advanced health and fitness certification in Canada for work with healthy and clinical populations. They are trained, certified, and insured to conduct the appraisals outlined in this proposal.

**Benefits:**

As a result of your participation in this study, you may receive the benefits of improved muscular strength and endurance in the trained muscle groups. You will also receive information regarding the current state of your cardiovascular health, which our research team can interpret for you.

**Rights and Welfare of the Individual:**

Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada, and the UPEI Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

You have the right to refuse to participate in this study. It is understood that you are free to withdraw from any or all parts of the study at any time without penalty. If you withdraw from the study, all data you have contributed will be destroyed upon request. Once all data have been submitted and identifiers removed, however, you will no longer have the opportunity to request that your data be removed from the study. Your identity will remain confidential as all individual records and results will be analyzed and referred to by number code only and kept in a locked cabinet in the Human Performance and Health Laboratory at the University of PEI. This lab will remain locked and only those directly involved in the study (namely Dr. Jamie Burr) will have access to your records and results. You will not be referred to by name in any study reports or research papers. Your individual results will remain confidential as they will not be discussed with anyone outside the research team.

Please be assured that you may ask questions at any time. We will be glad to discuss your results with you when they have become available and we welcome your comments and suggestions. Should you have any concerns about this study or wish further information, please contact Dr. Jamie Burr (902-620-5225) at the University of Prince Edward Island. If you have any concerns about your rights or treatment as a research subject, please contact the Research Subject Information Line in the University of PEI Research Ethics Board (902) 620-5104, or by e-mail at [reb@upei.ca](mailto:reb@upei.ca).



**PARTICIPANT CONSENT**

I, \_\_\_\_\_, understand the purpose and procedures of this investigation and consent to participate in this investigation.

I understand that at any time during the study, I will be free to withdraw without jeopardizing any of my educational opportunities. I understand that I do not waive my legal rights by signing the consent form. I will receive four pages of the consent form and understand the contents of the consent form, the proposed procedures and possible risks. I have had the opportunity to ask questions and have received satisfactory answers to all inquiries regarding this investigation. I will receive a signed and dated copy of the consent form upon request.

\_\_\_\_\_  
Printed Name of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

\_\_\_\_\_  
Printed Name of Witness

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Principal Investigator  
or/ designated representative

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Principal Investigator  
or/ designated representative

\_\_\_\_\_  
Date

# APPENDIX B: PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

CSEP approved Sept 12 2011 version

## PAR-Q+

### The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

#### SECTION 1 - GENERAL HEALTH

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.		YES	NO
1.	Has your doctor ever said that you have a heart condition OR high blood pressure?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	<input type="checkbox"/>	<input type="checkbox"/>
3.	Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	<input type="checkbox"/>	<input type="checkbox"/>
4.	Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Are you currently taking prescribed medications for a chronic medical condition?	<input type="checkbox"/>	<input type="checkbox"/>
6.	Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.	<input type="checkbox"/>	<input type="checkbox"/>
7.	Has your doctor ever said that you should only do medically supervised physical activity?	<input type="checkbox"/>	<input type="checkbox"/>

If you answered NO to all of the questions above, you are cleared for physical activity.



Go to Section 3 to sign the form. You do not need to complete Section 2.

- › Start becoming much more physically active – start slowly and build up gradually.
- › Follow the Canadian Physical Activity Guidelines for your age ([www.csep.ca/guidelines](http://www.csep.ca/guidelines)).
- › You may take part in a health and fitness appraisal.
- › If you have any further questions, contact a qualified exercise professional such as a CSEP Certified Exercise Physiologist\* (CSEP-CEP) or CSEP Certified Personal Trainer\* (CSEP-CPT).
- › If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.



If you answered YES to one or more of the questions above, please GO TO SECTION 2.



Delay becoming more active if:

- › You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- › You are pregnant – talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- › Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.

## SECTION 2 - CHRONIC MEDICAL CONDITIONS

Please read the questions below carefully and answer each one honestly: check YES or NO.		YES	NO
1.	Do you have Arthritis, Osteoporosis, or Back Problems?	<input type="checkbox"/> If yes, answer questions 1a-1c	<input type="checkbox"/> If no, go to question 2
1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	<input type="checkbox"/>	<input type="checkbox"/>
1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	<input type="checkbox"/>	<input type="checkbox"/>
1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Do you have Cancer of any kind?	<input type="checkbox"/> If yes, answer questions 2a-2b	<input type="checkbox"/> If no, go to question 3
2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?	<input type="checkbox"/>	<input type="checkbox"/>
2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	<input type="checkbox"/>	<input type="checkbox"/>
3.	Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm	<input type="checkbox"/> If yes, answer questions 3a-3e	<input type="checkbox"/> If no, go to question 4
3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	<input type="checkbox"/>	<input type="checkbox"/>
3b.	Do you have an irregular heart beat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)	<input type="checkbox"/>	<input type="checkbox"/>
3c.	Do you have chronic heart failure?	<input type="checkbox"/>	<input type="checkbox"/>
3d.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure)	<input type="checkbox"/>	<input type="checkbox"/>
3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	<input type="checkbox"/>	<input type="checkbox"/>
4.	Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes	<input type="checkbox"/> If yes, answer questions 4a-4c	<input type="checkbox"/> If no, go to question 5
4a.	Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure)	<input type="checkbox"/>	<input type="checkbox"/>
4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?	<input type="checkbox"/>	<input type="checkbox"/>
4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)	<input type="checkbox"/> If yes, answer questions 5a-5b	<input type="checkbox"/> If no, go to question 6
5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	<input type="checkbox"/>	<input type="checkbox"/>
5b.	Do you also have back problems affecting nerves or muscles?	<input type="checkbox"/>	<input type="checkbox"/>

Please read the questions below carefully and answer each one honestly: check YES or NO.		YES	NO
6.	Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure	<input type="checkbox"/> If yes, answer questions 6a-6d	<input type="checkbox"/> If no, go to question 7
6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	<input type="checkbox"/>	<input type="checkbox"/>
6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	<input type="checkbox"/>	<input type="checkbox"/>
6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	<input type="checkbox"/>	<input type="checkbox"/>
6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	<input type="checkbox"/>	<input type="checkbox"/>
7.	Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia	<input type="checkbox"/> If yes, answer questions 7a-7c	<input type="checkbox"/> If no, go to question 8
7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	<input type="checkbox"/>	<input type="checkbox"/>
7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	<input type="checkbox"/>	<input type="checkbox"/>
7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	<input type="checkbox"/>	<input type="checkbox"/>
8.	Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event	<input type="checkbox"/> If yes, answer questions 8a-c	<input type="checkbox"/> If no, go to question 9
8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	<input type="checkbox"/>	<input type="checkbox"/>
8b.	Do you have any impairment in walking or mobility?	<input type="checkbox"/>	<input type="checkbox"/>
8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	<input type="checkbox"/>	<input type="checkbox"/>
9.	Do you have any other medical condition not listed above or do you live with two chronic conditions?	<input type="checkbox"/> If yes, answer questions 9a-c	<input type="checkbox"/> If no, read the advice on page 4
9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?	<input type="checkbox"/>	<input type="checkbox"/>
9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	<input type="checkbox"/>	<input type="checkbox"/>
9c.	Do you currently live with two chronic conditions?	<input type="checkbox"/>	<input type="checkbox"/>

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.

# PAR-Q+



If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active:

- › It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
- › You are encouraged to start slowly and build up gradually – 20-60 min. of low- to moderate-intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- › As you progress, you should aim to accumulate 150 minutes or more of moderate-intensity physical activity per week.
- › If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.



If you answered YES to one or more of the follow-up questions about your medical condition:

- › You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a or qualified exercise professional (CSEP-CEP) for further information.



Delay becoming more active if:

- › You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- › You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- › Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

## SECTION 3 - DECLARATION

- › You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- › The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.
- › If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.
- › Please read and sign the declaration below:

*I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.*

NAME \_\_\_\_\_ DATE \_\_\_\_\_

SIGNATURE \_\_\_\_\_ WITNESS \_\_\_\_\_

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER \_\_\_\_\_

For more information, please contact:  
Canadian Society for Exercise Physiology  
[www.csep.ca](http://www.csep.ca)

### KEY REFERENCES

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The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or BC Ministry of Health Services.



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## APPENDIX C: Permission to Republish Figures

### WOLTERS KLUWER HEALTH, INC. LICENSE TERMS AND CONDITIONS

Jun 12, 2015

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## APPENDIX D:

The efficacy of blood flow restricted exercise: A systematic review & meta-analysis

Joshua Slys, Jack Stultz and Jamie F. Burr

<sup>1</sup> Human Performance and Health Research Laboratory, University of Prince Edward Island,  
Charlottetown PEI

### Abstract

**Objectives:** To systematically search and assess studies that have combined blood flow restriction (BFR) with exercise, and to perform meta-analysis of the reported results to quantify the effectiveness of BFR exercise on muscle strength and hypertrophy. **Methods:** A computer assisted database search was conducted for articles investigating the effect of exercise combined with BFR on muscle hypertrophy and strength. A total of 916 hits were screened in order based on title, abstract, and full article, resulting in 47 articles that fit the review criteria. **Results:** A total of 400 participants were included from 19 different studies measuring muscle strength increases when exercise is combined with BFR. Exercise was separated into aerobic and resistance exercise. Resulting from BFR aerobic exercise, there was a mean strength improvement of 0.4 Nm between the experimental group and control group, while BFR resistance exercise resulted in a mean improvement of 0.3kg. A total of 377 participants were included in 19 studies measuring muscle size increase (cross sectional area) when exercise was combined with BFR. The mean difference in muscle size between the experimental group and control group was 0.4cm<sup>2</sup>. **Conclusion:** Current evidence suggests that the addition of BFR to dynamic exercise training is effective for augmenting changes in both muscle strength and size. This effect was consistent for both resistance training and aerobically-based exercise, although the effect sizes

varied. The magnitude of observed changes are noteworthy, particularly considering the relatively short duration of the average intervention.

**Key words:** Occlusion, Ischemia, Kaatsu, Muscular Hypertrophy, Muscular Strength



## Introduction

The maintenance of skeletal muscle mass is an important factor for health, longevity, and quality of life<sup>52</sup>. Skeletal muscle is a major contributor to glycemic control acting as the body's largest glucose sink by mass, which accounts for approximately 80% of non-insulin stimulated glucose uptake<sup>53</sup> and also plays an important role in oxidizing fatty acids<sup>54</sup>. Adequate skeletal muscle is crucial to maintaining the ability to undertake activities of daily living, ambulation, and fall avoidance. At the other end of the physical activity spectrum, skeletal muscle quantity and quality have a direct bearing on sport performance<sup>55</sup>, basal metabolic rate, caloric expenditure, strength, power, and somatotype. Disuse of skeletal muscle leads to relatively rapid and progressive atrophy, decreases in oxidative capacity, fiber shortening and reduced muscle compliance; all of which result in a reduced exercise capacity, impaired immune system and decreased sensitivity to insulin<sup>56</sup>. As such, muscle strength and mass has important implications for both health and fitness.

To enhance both muscle mass and strength, high-intensity resistance exercise with loads approximating 70–85 % of one repetition maximum (1-RM) are typically recommended<sup>1</sup>. However, heavy-load resistance exercise is often challenging or even contraindicated for certain individuals, such as the elderly, persons with chronic disease, or rehabilitating and recovering athletes. As such, it is intriguing that several studies in recent years have suggested the potential for low load exercise (i.e. <25% maximal capacity) to stimulate significant muscular adaptations when the blood flow to a muscle or muscle group is restricted or fully occluded. For example, comparing blood flow restricted exercise to a non-occluded exercising control group, Takarada et al. (2000)<sup>57</sup> demonstrated a 14% increase in knee extensor strength of young subjects engaging in strength training at an intensity of 50% of 1 RM, while no change occurred using resistance training alone.

Blood flow restricted (BFR) training, also known as Kaatsu training, was pioneered by Yoshiaki Sato, of Japan in the 1970s and 1980s<sup>18</sup>. This training method involves decreasing blood flow to a muscle by application of an external constricting device, such as a blood pressure cuff or tourniquet, to provide mechanical compression of the underlying vasculature. BFR is applied with the intent to promote blood pooling in the capillary beds of the limb musculature distal the tourniquet<sup>6</sup>. Although there have been isolated reports of adverse events (as would be expected with any form of exercise), on the whole there is little published evidence to suggest that this type of training offers any greater health risk than typical dynamic exercise training with high loads<sup>58</sup>.

BFR alone has been shown to attenuate the disuse of atrophy during periods of immobilization<sup>59</sup>, however, BFR must be combined with an exercise stimulus for enhanced muscular development. The exercise stimulus of resistance exercise appears to provide the most substantial muscular gains when combined with BFR. Yet interestingly, several investigations have reported that low-intensity aerobic exercise combined with BFR can facilitate improvements in muscular size and strength, even though strength and hypertrophy do not typically occur from aerobic mode of exercise. The development of muscle size and strength using BFR-aerobic training may become a method of training for the wider population, including the frail and elderly.

There has been previous quality reviews<sup>60</sup> concerning BFR, however there has since been a fast growing evidence-base for BFR exercise training. Furthermore, the evidence has not been systematically reviewed. For these reasons, an up to date systematic review and meta-analysis of the BFR exercise training literature is needed for greater and more current understanding of the effects of blood flow restriction on training outcomes such as muscle strength and hypertrophic adaptations. This in turn will lead to the formulation of novel research questions and advance training methods for persons in both health and disease. At present, a variety of different BFR training methodologies are being employed and study designs have differed, making direct comparison challenging. Therefore, our objectives were: 1) to systematically identify and assess

studies that have combined blood flow restriction with exercise 2) to perform a meta-analysis to quantify the effectiveness of BFR exercise on muscle strength and hypertrophy 3) identify which BFR training methods result in the greatest strength and muscle hypertrophy outcomes.

## **Methods**

A computer assisted database search was used, targeting all articles published prior to the last week in June 2015. Databases searched included: PubMed, Medline, CAB abstracts, CINAHL, SPORT Discus, PSYCHinfo, and ScienceDirect. The search was conducted to find studies investigating the effect of exercise combined with BFR training on muscle hypertrophy and muscular strength. Search words included variations on words that were related to the restriction of blood flow to skeletal muscle, types of exercise used with BFR, and possible effects caused by BFR. The search terms used are included as a supplemental file to this article (Table 1, supplemental material). Articles retrieved were examined for further relevant references.

All included articles were published in peer-reviewed English language scientific journals. Any investigation that focused on a BFR intervention combined with an exercise stimulus and compared to a matched exercise exposure without BFR was eligible for inclusion. At least one of two outcomes must have been considered: muscle strength or muscle size. Only studies using human adult (>18yr) human participants in ostensibly good health were included. No modality of exercise was excluded but were classified as either an aerobic or resistance modality. Given the evidence relating to the differing physiological effects elicited by these two modalities (from both a clinical and performance standpoint), the authors believe this is a necessary division for interpretation. Article exclusion criteria included published supplements, abstracts, reports, reviews, opinion articles, commentaries, magazine articles, book chapters, case studies and presentations; however, relevant peripheral literature was collected and reference lists were searched. Only studies using mechanical blood flow restriction through external applied pressure

on the proximal point of a limb (i.e blood pressure cuff or tourniquet) were included. All other mechanisms (e.g. hyperbaric chamber, hypoxic environment) were excluded. Mechanisms employing altered atmospheric pressure or reduced partial pressure of O<sub>2</sub> were excluded due to variability introduced from the physiologic adaptation happening via the lung or other components of the cardiorespiratory system, not related to a localized stimulus. The authors believe that the specificity and utility of the results for assessing BFR training are improved by the exclusion of such studies.

A total of 916 hits across all databases were saved in a reference management software program wherein exact duplicates were removed, leaving a total of 820 articles. Two of the authors (JS and JS) independently screened articles based on the title and abstract of each and the full article was retrieved for review when relevance was unclear from this information. In the event of a disagreement as to article's relevance by the primary reviewers the third author's judgment was used as the sway vote. The reason for removal of studies, which were captured then culled were 1) improper controls or randomization to assess efficacy, and 2) not fully meeting our inclusion criteria (see above). This resulted in 47 articles that fit the inclusion criteria for the systematic review. All remaining articles were assessed for methodological quality using the Downs and Black checklist (1998)<sup>61</sup> (Table 2, supplemental material). Articles that reported their results as a percentage change or only in graphical form could not be included in the meta-analysis due to an inability to accurately calculate an effect size. A total of 28 studies met the full inclusion criteria for the meta-analysis. The process of article retrieval is outlined in Figure 1.



*Fig 1: Flowchart demonstrating the step-by-step process of article elimination to find the final articles to be included in the systematic review.*

The extracted data included study identifying information, year of publication, research design, objectives, participant characteristics (age, sex, health status), sample size, intervention, FITT (frequency, intensity, time and type of exercise), methods of assessment, and physiological results.

Descriptive statistics for each study and effect sizes (ES) were calculated using Comprehensive Meta-Analysis software (V.2.0, Biostat, Inc., Englewood, NJ). ES were analyzed and

appropriately adjusted for potential sample bias using the methodology of Duval and Tweedie (2000)<sup>62</sup>. ES calculations were performed using unmatched groups and post data only; post data included means, SD, and sample size. A level of significance of  $P = 0.05$  was selected *a priori* and the scale proposed by Rhea (2004)<sup>63</sup> was used for interpretation of effect size magnitude. Exercise was represented by both aerobic and resistance modalities. Almost uniformly, studies that tested aerobic exercise quantified BFR related increases in strength using Newton meters (Nm); whereas studies that used resistance exercise quantified increases in strength using a measure of performance (i.e. weight lifted in kg). As such, exercise modalities were considered separately for both practical and theoretical reasons. Similarly, a mean difference for mixed modality training protocols could not be calculated, and the data is thus presented below separately.

## **Results**

The 47 studies identified that fit the inclusion criteria for the systematic review included all healthy participants that had a mean age of  $34 \pm 18$  yrs (18-70). There were 26 male only studies, 7 female only studies, and 14 studies that included both male and female.

### **Muscular strength**

A total of 400 participants were included from 19 different studies (41 cases) measuring muscular strength increases and considering exercise combined with blood flow restriction.

Amongst the total of 72 subjects representing 4 independent studies (14 cases) that considered strength changes resulting from BFR aerobic exercise, the mean improvement in strength gains of

the experimental group above changes in the control group was 0.4 Nm [95% CI: 0.1, 0.6;  $p=0.04$ ] (Fig. 2A). Typically, when aerobic training was combined with BFR, muscle strength increased 5-8Nm. Training more than 6 weeks increased the mean difference in muscle strength between the experimental group and control group more than training less than 6 week, 0.6Nm [95% CI: 0.4, 0.9] versus 0.2Nm [95% CI: -0.5, 0.2], respectively ( $p=0.03$ ). The mean increase in muscle strength between the experimental group and the control group was larger when walking intensity was greater than 70m/min compared to an intensity of less then 70m/min, 1.9 Nm [95% CI: 1.4, 2.3] vs. -0.2 [95% CI: -0.5, -0.2], respectively ( $p<0.001$ ). There was inadequate data to analyze other training variables within aerobic-BFR training.

There were 15 studies (27 cases) with a total of 328 subjects, that considered strength changes resulting from BFR resistance exercise, and these revealed a mean augmentation of muscle strength gains between the experimental group and control group of an additional 0.3kg [95% CI: 0.1, 0.5,  $p<0.01$ ] (Fig 2B). Only a minor variation was apparent in the mean difference in gains comparing the experimental and control group considering 2 day versus 3 day/week training, 0.4kg [95% CI: -0.2, 1.0] versus 0.3kg [95% CI: 0.01, 0.4], respectively ( $p>0.05$ ). Gains in muscle strength were significantly greater when the intensity of the workout was  $>20\%$  1RM versus  $<20\%$ 1RM or lower. Importantly, when comparing gains in muscle strength between training at 20% 1RM and 30%1RM, training at 30%1RM resulted in a much greater improvement in muscle strength ( $p<0.001$ ). Training programs of greater than 8wk were approximately 60% as effective as those less than 8wk (0.2kg vs. 0.3kg,  $p=0.05$ ), but it should be noted that the mean difference between the experimental and control group were relatively small and despite statistical significance, practical significance may be of more questionable value. Cuff pressure of  $\geq 150\text{mmHg}$  caused an increase in strength comparing the experimental group and control group than when the cuff pressure was lower than 150mmHg, 0.2kg [95% CI: -0.1, 0.5] versus 0.1kg [95% CI: -0.2, 0.4], respectively ( $p>0.05$ ).

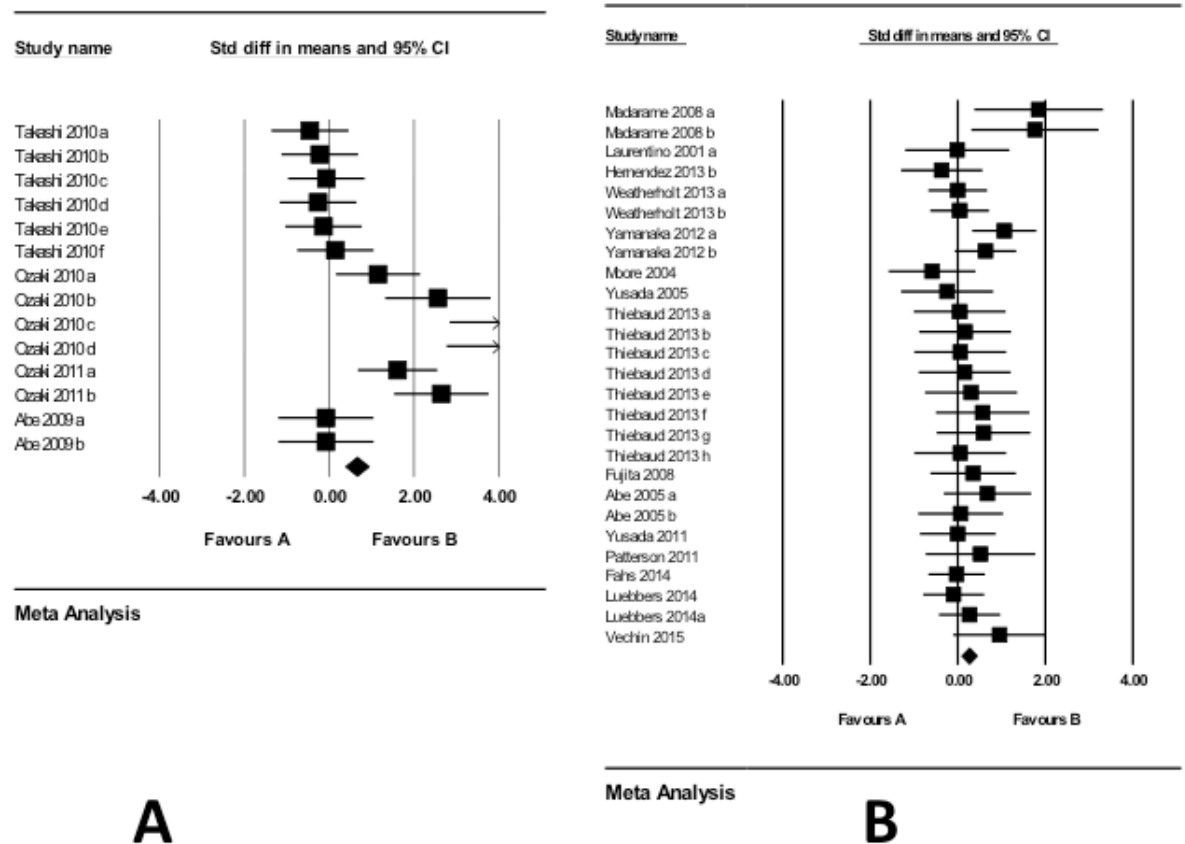


Fig 2: Forrester Plot displaying the difference in muscle strength between the experimental group and control group for each individual case, when undergoing aerobic exercise ("A") and resistance exercise ("B").

### Muscular hypertrophy

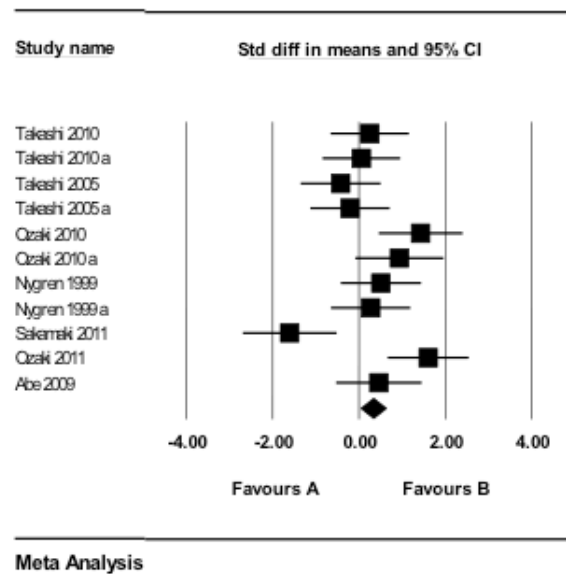
A total of 377 participants were included in 19 studies (40 cases) measuring muscle size increase (cross sectional area (CSA)) considering both modalities of exercise when combined with blood flow restriction. Most often, the change in muscle size ranged from an increase of 2-5cm<sup>2</sup> when exercise was combined with BFR. The mean increase in post-training muscle size between the



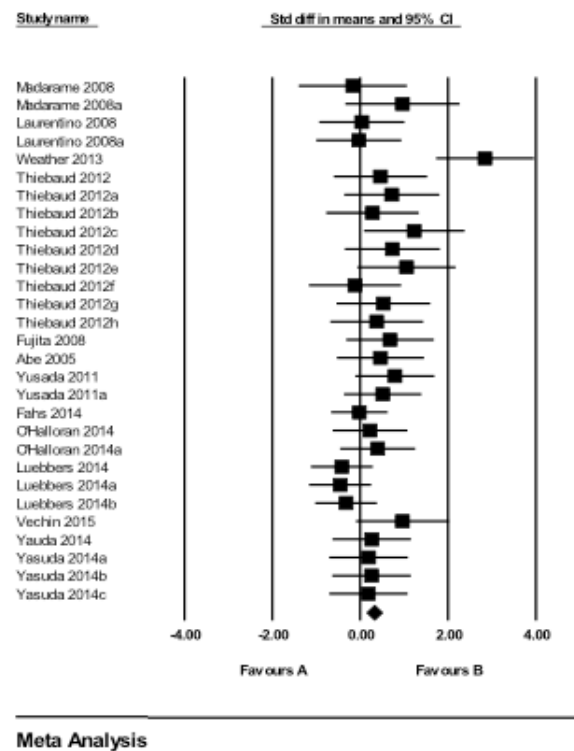
experimental group and the control group was  $0.36\text{cm}^2$  [95% CI: 0.16, 0.46,  $p<0.001$ ]. Training programs that were 8 weeks or longer caused a  $0.7\text{ cm}^2$  [95% CI: 0.34, 0.964] size increase between experimental and control group, compared to training programs 8 weeks or less that only caused a  $0.2\text{cm}^2$  (95% CI: -0.10, 0.37) size difference ( $p<0.001$ ). Muscle size differences between the experimental group and control group did vary when training took place 3 days a week compared to a training 2 days a week,  $0.34\text{cm}^2$  [95% CI: 0.11, 56] versus  $0.29\text{cm}^2$  [95% CI: 0.031 0.55], respectively ( $p>0.05$ ).

A total of 131 participants were included in 7 studies (11 cases) measuring CSA increase when aerobic exercise is combined with blood flow restriction. Aerobic training had a mean increase of post-training muscle size between the experimental group and control group of  $0.32\text{cm}^2$   $p = 0.03$  [95% CI: 0.03, 0.61] (Fig. 3A). There were insufficient studies to analyze further dose-response training variables within aerobic-BFR training.

A total of 246 participants were included in 12 studies (29 cases) measuring CSA increase when resistance exercise was combined with blood flow restriction. The mean increase in muscle size as a result of BFR training was  $0.41\text{cm}^2$ ,  $p=0.001$  [95% CI: 0.12, 0.58] (Fig. 3B) greater than that seen in the control groups.



A



B

Fig 3: Forrest Plot displaying the difference in muscle size between the experimental group and control group for each individual case, when undergoing aerobic exercise ("A") resistance exercise ("B").

## Discussion

Current research suggests that the addition of BFR to low load dynamic exercise training is effective for augmenting changes in both muscle strength and size. This effect was true for both resistance-training exercises and aerobically based exercise, although the degree of increase varied. Importantly, research suggests that low load resistance exercise (20-30%1RM) and low

load aerobic exercise (<70m/min walk training), which would not be expected to cause considerable increases in muscular quantity or quality under normal circumstances, when combined with BFR produced an exaggerated response for maximizing muscle strength and hypertrophy. This analysis offers a quantified description of the strength increase produced by various training variables including intensity, frequency, volume, and cuff pressure. At present, there remain a number of further variables that lack a sufficient evidence base to be included in meta-analysis. This highlights the need for further work in this area to clarify the dose-response relationship of this perturbation of typical exercise training; however, the results of this analysis give insight into variables and methodological considerations that could be important to consider in future research design. Furthermore, the authors highlight that the identification and analysis of these variables is based on limited research, using specific equipment, and should be interpreted with caution.

### **Muscular strength**

Owing to a methodological difference in the reporting of units of strength between aerobic and resistance modalities of exercise, we were unable to calculate an “overall” effect for exercise irrespective of the stimulus. However, since both aerobic and resistance modalities revealed a positive mean difference between the experimental and control group, it seems acceptable to conclude that, regardless of the unit of measure, overall muscle strength would also have a mean increase.

Our analysis suggests that when performing BFR aerobic exercise, training durations >6 weeks produced greater strength increases compared to training <6 weeks. This is in agreement with the generally accepted adaptation period for standard resistance training, and the work of Loenneke<sup>60</sup> et al (2012), who have suggested that with BFR training, muscle strength does not significantly increase until the 10<sup>th</sup> week.

The current evidence base suggests that as a result of BFR resistance training, greater strength gains may be expected when employing intensities  $\geq 20\%1RM$ . Such an effect mirrors what would be expected for traditional resistance training, albeit at a greatly reduced percentage of 1RM. Despite a greater overall efficacy with higher loads, however, it is important to highlight that measurable effects were still consistently observed even when training employed these very low intensities, which would not be expected to illicit adaptation in the absence of BFR. It is entirely possible that efficacy may change further using higher intensities, or that risk may appreciably increase, but at present this remains speculation.

From our analysis, BFR training trended toward greater efficacy for increasing muscle strength when cuff pressure  $>150\text{mmHg}$ , but the 95% confidence interval crosses zero thus this should be interpreted cautiously. Within the literature there are many different cuff pressures used for BFR training. It has been found that there is no single pressure that produces equal BFR between subjects, and different types of cuffs and limb circumferences occlude arterial blood flow at much different inflation pressures<sup>64</sup>. Therefore, there is a need for more investigation into a model that will result in equal occlusion for all subjects. We do not believe the above cut-points to represent hard-fast thresholds, but rather these apparent divides in common methodologies were the only points at which an analysis could be performed between variables. Nonetheless, this may represent important information when selecting application methods to use with BFR training.

### **Muscular hypertrophy**

Perhaps not surprisingly, the evidence suggests that resistance training causes greater increases in muscle size than aerobic training. This difference is likely related to the purposeful isolation and increased muscular work performed by a given muscle group in resistance training.

Overall,  $\geq 8\text{wk}$  of training has a greater effect on muscle size than training  $< 8\text{wk}$ . In agreement with muscle strength, a cuff pressure  $>150\text{mmHg}$  appeared more effective at increasing muscle

size than pressures < 150mmHg, but further investigation into the optimization of cuff pressure and the relationship with other training variables (and safety) is again suggested. There were insufficient studies to further breakdown and analyze the training variables of resistance and aerobic exercise.

## **Conclusion**

This systematic review provides meta-analytic evidence of greater increases in muscle size and strength when exercise is combined with BFR, compared with low load exercise alone. Given that the training intensity typically required to maximize increases in strength and hypertrophy ranges from 45%-60% 1RM in untrained individuals, or 80%-85% 1RM in trained athletes, the accumulated evidence showing alterations in strength and hypertrophy with low loads (20%-50% 1RM), is convincing verification that BFR contributes substantially to these adaptive processes. This type of training offers potential benefits to various practitioners ranging from clinical to human performance applications. Low load training may offer benefit to those recovering from orthopaedic or other conditions requiring rehabilitative care, but for which higher load training is contraindicated. Similarly, the practitioner working with athletes may find application in progressing strength while reducing loads on the associated tissues including muscular, tendinous and bony. Finally, it is worth stressing that the current findings regarding optimal training methods should be interpreted with the understanding that few studies have specifically sought to determine these factors as targeted study outcomes. A strength of the systematic reviewing process is the ability to highlight knowledge gaps and this has revealed that, at present, there is a relative dearth of specific research in this area; thus, more targeted studies are required before concrete statements regarding methodological optimization can be made. Again, the above cut-points chosen were apparent divides in common methodologies of the literature and were the only cut-points at which an analysis could be performed between variables, which we offer as a starting point. We do not believe these cut-points represent hard-fast thresholds; nonetheless, this

is a good stepping off point for future research as this review has highlighted important areas for which further research is necessary.

### **Practical implications**

- These results suggest lighter load BFR training to stimulate increases in muscle size and strength effects may be effective, and could potentially be used when traditional high-load training may be inappropriate or unattainable
- Current evidence suggests that within the range of low load stimulus, adaptation may still be associated with intensity (i.e. at 30%1RM could offer much more strength gaining benefit than training at 20% 1RM)
- Quantifiable muscular adaptations present quickly; however, training durations >6 weeks seem to offer greater returns in strength adaptation.
- Benefit to those recovering from orthopaedic or other conditions requiring rehabilitative care, but for which higher load training is contraindicated.
- Application in progressing strength while reducing loads on the associated tissues including muscular, tendinous and bony.

